APPROVAL ORDER

OOM-0579

AAV 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JAN 28 2000

Larry A. Kroger, Ph.D.
Senior Regulatory Programs Manager
GE Medical Systems
General Electric Company
P.O. Box 414
Milwaukee, WI 53201

Re: P990066
Senographe 2000 D Full Field Digital Mammography System
Filed: October 29, 1999
Amended: Dec.10 and Dec. 13, 1999

Dear Dr. Kroger:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Senographe 2000 D Full Field Digital Mammography System. This device is indicated for generating mammographic images that can be used for screening and diagnosis of breast cancer. The Senographe 2000 D is intended to be used in the same clinical applications as traditional mammographic film-screen systems. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. Until such time as an FDA approved accreditation process for full-field digital mammography has been developed the Senographe 2000 D Full Field Digital Mammography System must only be sold to screen-film accredited/certified facilities. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact John C. Monahan at (301) 594-1212.

Sincerely yours,

David W. Feigal, Jr., M.D.
Acting Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b)has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3)Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

(1)May have caused or contributed to a death or serious injury; or

(2)Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name	Digital Mammographic X-ray System
Device Trade Name	Senographe 2000D
Applicant's Name and Address	GE Medical Systems 3000 N. Grandview Blvd. W-709 Waukesha, WI 53188
PMA Number:	P990066
Date of Panel Recommendation:	December 16, 1999
Date of Good Manufacturing Practices Inspection:	December 6-9, 1999
Date of Notice of Approval to the Applicant:	January 28, 2000

II. INDICATIONS FOR USE

The Senographe 2000D system generates digital mammographic images that can be used for screening and in the diagnosis of breast cancer. The Senographe 2000D is intended to be used in the same clinical applications as traditional film-based mammographic systems.

III. DEVICE DESCRIPTION

The Senographe 2000D is equipped with a dual track X-ray tube (molybdenum/rhodium) and a digital detector. The digital detector is a flat panel of amorphous silicon on which the cesium iodide is deposited to maximize detection of X-rays. Positioning operations and X-ray exposure are controlled by the Control Panel, which also controls power to all parts of the Senographe 2000D system. The Senographe 2000D includes an acquisition work station ("AWS") monitor, keyboard and mouse, computer, electronics, accessory storage, and uninterruptable power supply. The AWS is used for image acquisition, processing, and display. The AWS can also be used for database management and can send images to archive, review, or filming. The device utilizes a hard-copy laser-film writer for image presentation. The printer window widths and window level are set automatically or can be user adjusted prior to printing. Images are displayed per film 1x1.

Several options are available for use with the Senographe 2000D system. These options include a FFDM review workstation, a mass archiving system, a laser camera, networking capabilities and CD-ROM interchange media. The Senographe 2000D review workstation is a stand-alone workstation with its own dedicated computer and image database. The review workstation supports image display, manipulation, and film composing functions.

IV. CONTRAINDICATIONS

None known

V. WARNINGS and PRECAUTIONS

For User

Senographe 2000D

- For U.S. only, until such time as an FDA approved accreditation process for full-field digital mammography has been developed, the Senographe 2000D Full Field Digital Mammography System must only be used in MQSA screen-film accredited/certified facilities.
- The light box (on the AWS cart) must *not* be used for final interpretation of examinations. The ambient light conditions in the examination room, and the resulting light level of the light box, are incompatible with its use for final interpretations.
- The (AWS) workstation monitor must *not* be used for final interpretation of examinations. It is set up for optimum visualization with an ambient light level of 50 lux. Leaving the AWS light box illuminated without a film in place may degrade reviewing quality of images displayed on the monitor.
- Only images produced by GE-recommended laser cameras can be used for final interpretation of examinations. For compatible printers, see the latest product data sheets for this system, which you can obtain from your local sales representative.
- The three-section table is not designed to hold items in excess of 20 kg weight.
- Never make a clinical examination without either the Bucky or the Breast Holder or the Magnification stand fitted; the unprotected edge of the Digital Detector may damage sensitive skin when compression is applied.
- Breast compression of at least 3 daN (30 Newtons or 6.7 pounds) is essential in AOP mode.
- The AWS Cart is mounted on wheels so that it can be easily positioned for maximum convenience in the examination room. It should NOT be considered a "mobile" unit. Take great care if you must move it in the vicinity of any person or equipment. Do not move it during an examination.
- The monitor should be used in a suitably dark environment when reviewing a digital image. The optimum ambient light level is 50 lux.
- NEVER switch off at the Uninterruptible Power Supply (UPS) except in emergency (risk of data loss).
- To assure continued high level operation of the Senographe 2000D, the recommended quality control procedures should be followed.
- All measurement values refer to measurements made at the image plane. When magnification mode is used, the zoom factor is NOT taken into account. All processed images in Medical Application are in log format. All raw images in RWS are in linear format. The displayed measurements represent the lengths and areas of the graphic annotations made by the user, not the real length or surface area of the pathologies displayed on the screen.
- Annotations added by the operator on the Acquisition Workstation will be lost during image transfer to the Review Workstation.
- In AOP mode, only use a 19 x 23 cm paddle. The use of all other paddles is only permitted in Manual mode. In AOP mode, the automatic calculation of administered dose will only be accurate if the 19 x

23 cm paddle (specific to the Senographe 2000D) is used. Paddles that are NOT to be used in AOP mode are labeled with the following symbols:

- Markers larger than 2 mm^2 should not be present in the ROI. Large markers will affect the calculation of tissue density, which may lead to a degraded image.

- After exposure press  (located on the right of the Control Console) for decompression if the automatic decompression is not set in the program.

- In the absence of the compression paddle, leave the space free between the bottom of the paddle arm and the top of the image receptor assembly.

- To avoid image loss, never touch the recordable surface of a recordable CD (CD-R). Handle the disk only by the outer edge. Do not place it face down on a hard surface. Fingerprints or scratches will make the disk unusable. Before usage, verify that CD-R surface has no visible scratches. If there are any scratches, do NOT use the CD-R.

Senographe 2000D Review Workstation

- The Senographe 2000D Review Workstation has not been cleared by the FDA for final interpretation of examinations. Final interpretations should be done from hard copy films only.

- The monitor should be used in a sufficiently dark environment (optimum ambient light level of 50 lux) when reading a digital image.

- Should it ever be necessary to remove all power from the workstation (for maintenance, or to move the workstation), workstation database corruption may occur if the following procedure is not used: You MUST first bring the workstation to the **Shutdown** state as described in Section 3 of the Operator's Manual. Once the system is completely shut down, switch off the equipment in this order: workstation computer unit; monitors; external CD-ROM device; external hard disk unit (option); filming interface unit (option); and keypad.

- When saving images on a CD, it is strongly recommended that no other operation should be performed. For a full CD-R the save operation can take up to 45 minutes.

For Device

Senographe 2000D

- If the digital detector casing is punctured, it must be removed by authorized GE Service personnel wearing protective gloves and dust masks; send the protective items for disposal along with the defective detector.

- Only Senographe 2000D recommended accessories should be used with this equipment. Failure to heed this warning may cause unexpected functions and possible data loss.

- Software programs other than those supplied by General Electric Medical Systems specifically for use with this system must NOT be loaded onto the system.

- The Interchange Media option is NOT recommended for permanent archiving. GE does not guarantee the suitability of the media for such purposes.

Senographe 2000D Review Workstation

- The Interchange Media option is NOT recommended for permanent archiving. GE does not guarantee the suitability of the media for such purposes.

- The Review Workstation monitors are unshielded. Placing them in a high magnetic field (e.g., near an MR system magnet) can cause permanent damage, and may void the warranty.

For Cleaning And Disinfection

Senographe 2000D

- CIDEX (a cleaning solution) contains glutaraldehyde. Direct contact is corrosive to exposed tissue, causing eye damage and skin irritation/damage. Do not get into eyes, on skin or on clothing. Use in well ventilated area and store in closed containers.

- Adequate cleaning and disinfection is necessary to prevent disease transmission. Be sure to thoroughly clean and disinfect equipment surfaces that contact the patient and all equipment surfaces likely to become soiled during use.

- Improper cleaning methods or the use of certain cleaning and disinfecting agents can damage the equipment, cause poor imaging performance or increase the risk of electric shock. To avoid possible injury or equipment damage:

  — Do not use harsh detergents, abrasive cleaners, high alcohol concentration or Methanol at any concentration. If skin preparations contain high alcohol concentrations, allow sufficient drying time before applying compression;

  — Do not expose equipment parts to steam or high temperature sterilization;

  — Never allow liquids to enter the internal parts of the equipment. Do not apply cleaning sprays or liquids directly to the equipment; always use a clean cloth dampened with the spray or liquid. If you become aware of liquid entry, disconnect the electrical supply and have the equipment checked by qualified service personnel before returning it to use.

- Always follow the germicide manufacturer's instructions and precautions for mixing, storage, method of application, contact time, rinsing requirements, protective clothing, shelf life and disposal to help assure effective and safe use of the product.

VI. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

No serious adverse events were reported for the patients enrolled in the clinical study. However excessive breast compression, excessive X-ray exposure, electric shock, infection and skin irritation, abrasion or puncture wounds are potential adverse effects of mammography.

VII. ALTERNATIVE PRACTICES AND PROCEDURES

There are several methods available for screening and diagnosing cancer in the breast. These include the following: clinical breast examination; film-screen mammography; ultrasound examination; magnetic resonance imaging; and xeromammography. After an abnormality is detected, a biopsy may be performed to diagnose the cancer.

VIII. MARKETING HISTORY

The Senographe 2000D is currently marketed in all Europeans countries, Canada, all Latin American countries (except Mexico), and all Asian countries. No Senographe 2000D has been withdrawn from marketing for reasons related to the safety or effectiveness of the device.

IX. SUMMARY OF NONCLINICAL STUDIES

The sponsor performed several tests to document image and detector parameters and, in some cases, compare them to the results of screen film systems.

A. Comparison of Dynamic Range and Sensitometric Response for Screen Film Mammography (SFM) and Senographe 2000D

Figure 1. Response curve of the Digital Detector

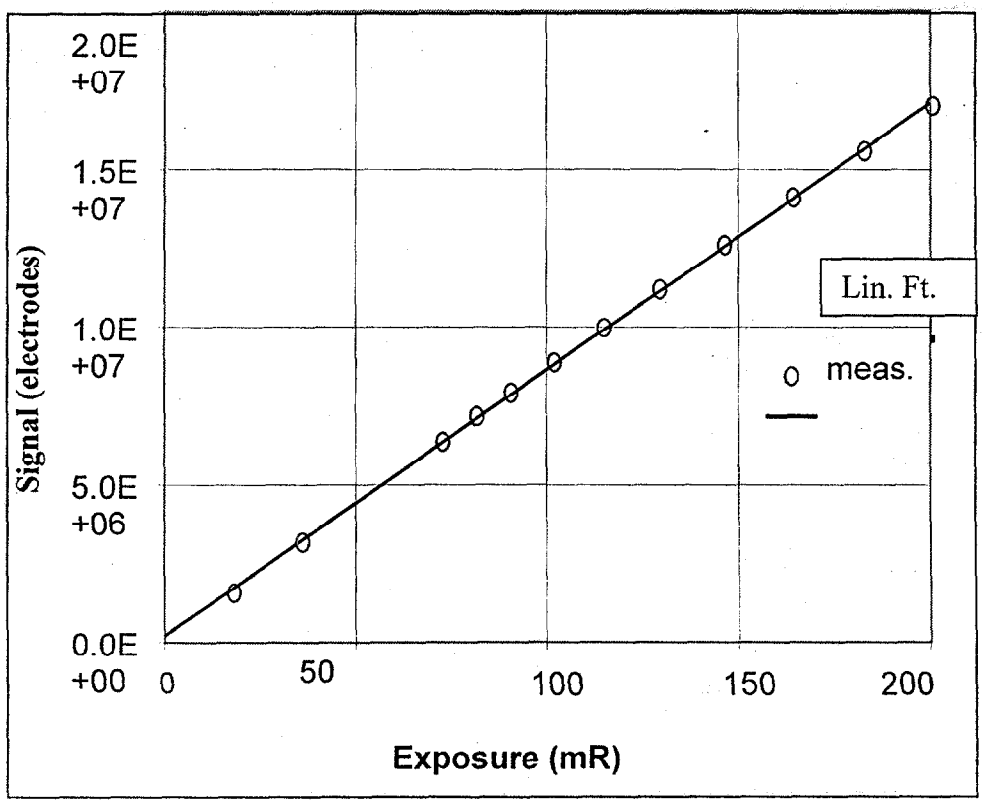
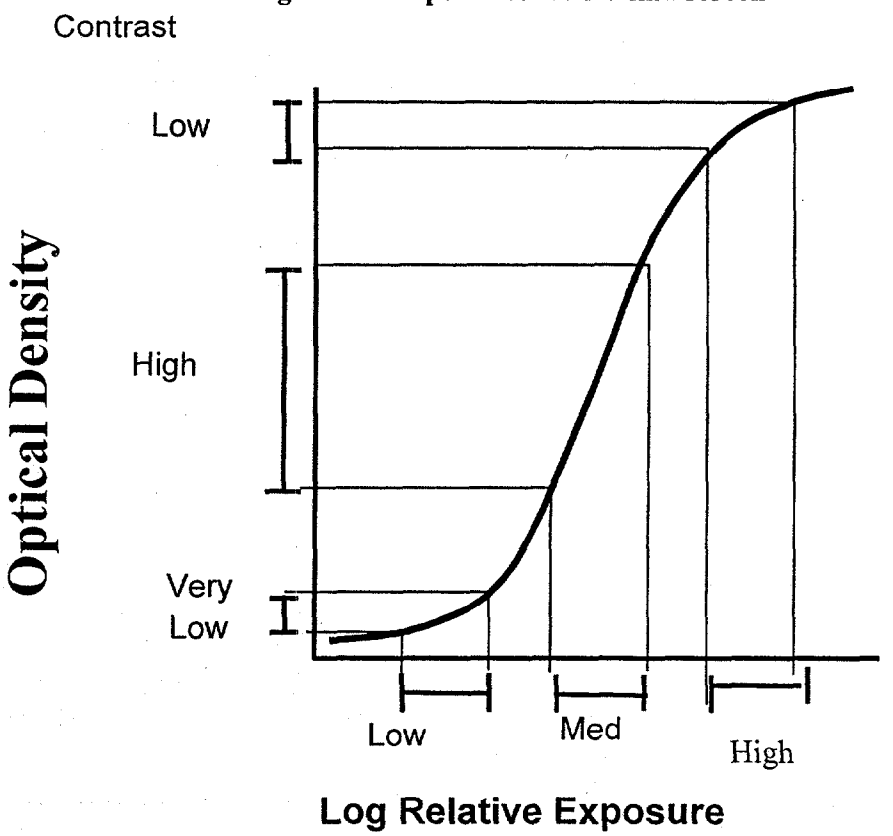


Figure 2. Response curve for film screen



The solid-state detector exhibits a response that is linear over a range of 0 to 153 mR at the breast support surface. The range of exposure over which linear response is achieved is at least 3 times larger than the linear portion of the SFM sensitometric curve as seen in Figures 1 and 2.

B. Comparison of Senographe 2000D and SFM DQE

Definition of Detective Quantum Efficiency (DQE)

DQE measures the efficiency by which a system transfers both signal and noise. It is defined as the ratio of the squares of signal-to-noise ratios (SNRs). Since the output SNR is a measure of the displayed image quality and the input SNR can be related to patient dose, DQE can be considered as a ratio of image quality to patient dose. Doubling DQE means that Senographe 2000D has the same image quality at half the dose. Therefore Senographe 2000D yields a 40% improvement in image quality.

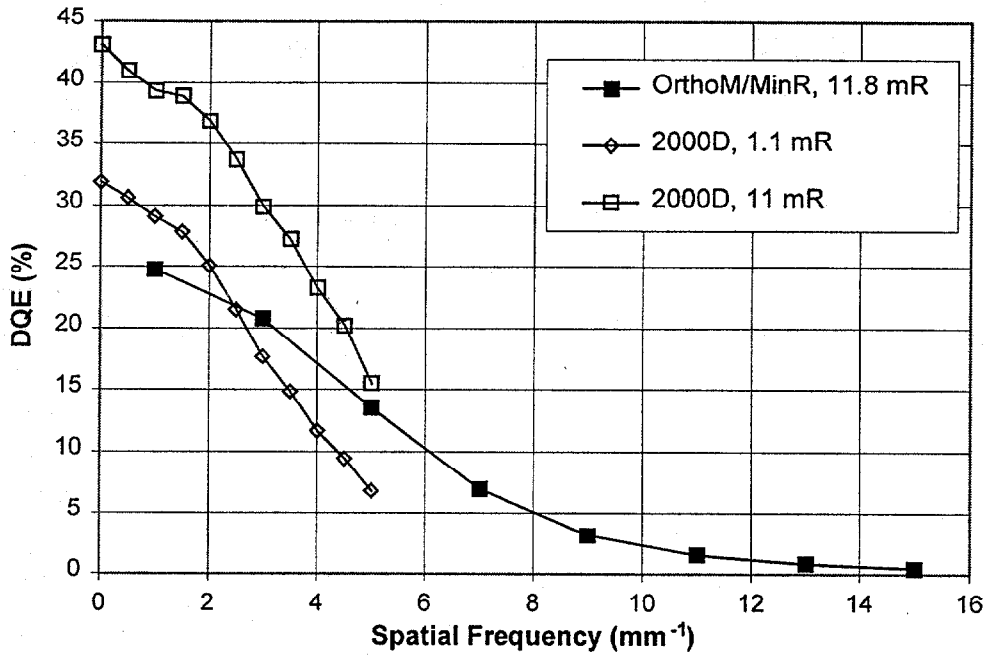
$$DQE = \frac{SNR^2 \text{ at detector output}}{SNR^2 \text{ at detector input}} \propto \frac{\text{Image Quality}}{\text{Patient Dose}}$$

where SNR = signal-to-noise ratio

Comparison

The sponsor measured the DQE for the Senograph 2000D and for a screen-film system. These measurements are shown in Figure 3.

Figure 3. DQE of the Senographe 2000D and a Screen-Film System



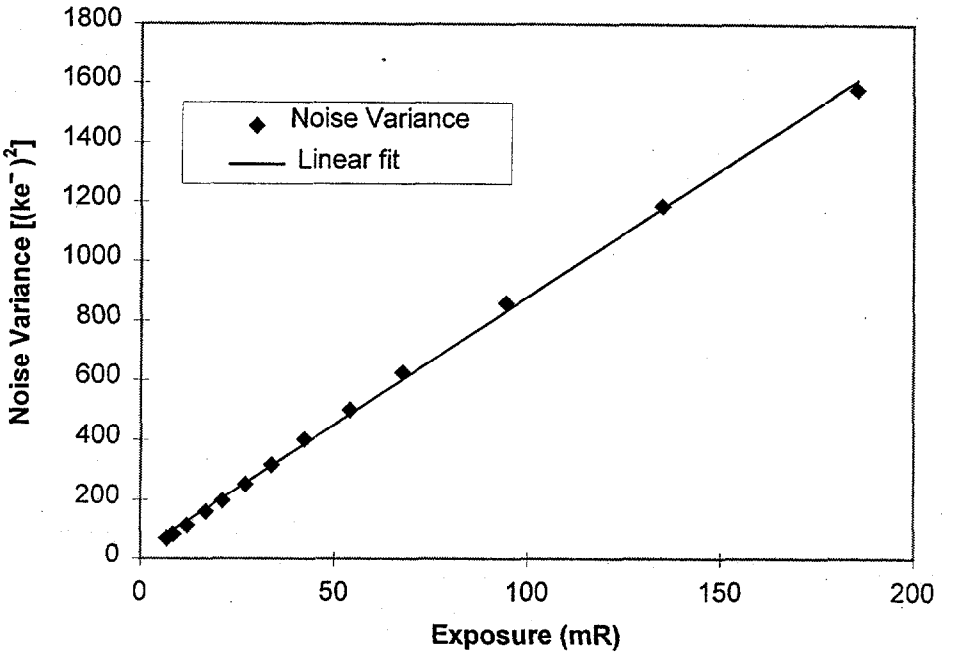
All Senographe 2000D DQE measurements shown here were made using 30 kVp, Rh anode track, Rh filter, and added filtration of 1.5 cm acrylic plus 33 mm Al. Exposures at the detector entrance plane are included with the data.

At detector exposure levels characteristic of those used in screen-film mammography (10 to 15 mR), the DQE of the Senographe 2000D exceeds that of common screen-film systems throughout the 0 to 5 lp/mm range. Even at 1 mR, the low-frequency DQE of the Senographe 2000D exceeds that of screen-film systems when used at ten times the exposure level. While the DQE of screen-film systems extends to higher spatial frequencies, film-grain noise and not quantum noise often dominate the output SNR. Because of the essentially linear response of the Senographe 2000D detector, quantum-limited performance and substantially constant DQE are achieved over a wide range of exposure levels.

C. DQE versus Exposure Level - Quantum-Limited Performance

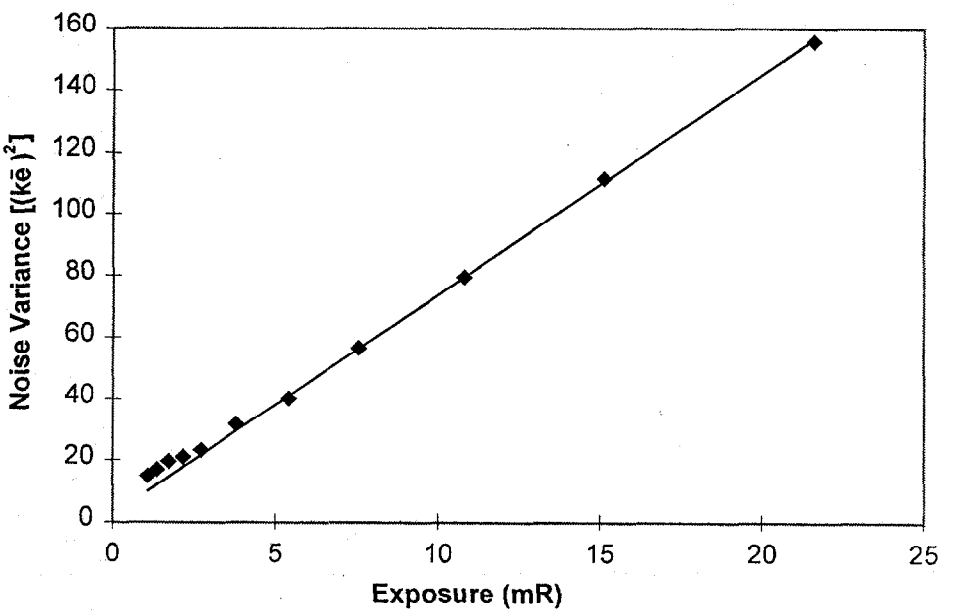
The detector of the Senographe 2000D not only exhibits a linear signal response over a wide exposure range, it also exhibits a quantum-limited noise response. Quantum-limited response is evidenced by image noise variance (the square of the standard deviation of the pixel values within a region of interest) that increases linearly with the exposure to the detector (Fig. 4).

Figure 4. Image Noise vs. Exposure for the Senographe 2000D



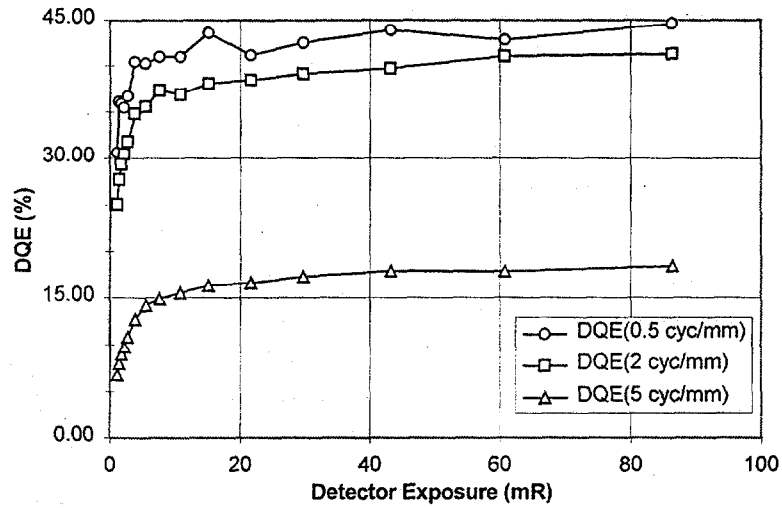
At low exposure levels, the plot of image noise variance vs. exposure commonly deviates from a straight line due to the influence of noise in the imaging system. For the Senographe 2000D, this deviation is not evident until the exposure at the detector is less than about 3 mR (Fig. 5).

Figure 5. Image Noise vs. Exposure for the Senographe 2000D



The combination of linear signal response and quantum-limited noise response leads to a DQE that is independent of exposure level over a broad range of exposures. Screen-film systems tend to have low DQE at high film densities (near the skin line) and at low film densities (in the image of glandular tissue or near the chest wall), the Senographe 2000D provides uniformly high DQE throughout the mammogram (Fig. 6). This provides a probability of detection of an abnormality that is less dependent on its location than is the case for screen-film detectors.

Figure 6. DQE vs. Exposure at Three Spatial Frequencies



DQE is essentially independent of exposure for exposures at the detector plane greater than about 3 mR. Therefore, Senographe 2000D DQE has little dependence on the exposure level for the clinical exposure range.

D. Summary of findings from the Preclinical Studies

The range of linear signal response for the Senographe 2000D is significantly better than that of screen film.

The detective quantum efficiency (DQE) for the Senographe 2000D is comparable to or higher than screen film up to its Nyquist frequency (5 lp/mm), though beyond that frequency the Senographe 2000D gives no meaningful information.

Below the Nyquist frequency, for exposures that are typical near the skin line or in a dense area of the breast, the Senographe 2000D has a DQE that is higher than that of screen-film by a factor of 2 to10. Furthermore, at these spatial frequencies the Senographe 2000D has nearly constant DQE over the range of exposures commonly found in a mammogram, while that of screen-film varies by a factor of 3 to 5 between the mid- and high-density regions

While the higher DQE for the Senographe 2000D at spatial frequencies less than or equal to the Nyquist frequency suggests the possibility that mammograms may be taken at a lower radiation dose, particularly in dense breasted women, the accuracy of mammographic interpretation at lower doses has not been studied to determine whether the absence of information above the Nyquist frequency is clinically important.

The combination of linear signal response and quantum-limited noise response leads to a DQE that is independent of exposure level over a broad range of exposures. Unlike screen-film systems, which tend to have low DQE at high film densities (near the skin line) and at low film densities (in the image of glandular tissue or near the chest wall), the Senographe 2000D provides uniformly high DQE throughout the mammogram. This provides a probability of detection of an abnormality that is less dependent on its

location than is the case for screen-film detectors. This was shown to be true by the side-by-side feature comparison (see section I of CLINICAL STUDIES).

The Senographe 2000D has wider exposure latitudes, higher DQE, allows for electronic archival transmission and image manipulation, and involves shorter examination time. The ability to manipulate images has the potential to eliminate the need for additional magnification of views. Similarly, windowing and leveling can compensate for exposure variations eliminating the need for repeated exposures or exposures adjusted to specifically view the skin line or the chest wall.

X. SUMMARY OF CLINICAL STUDIES

READER STUDY DATA

Four clinical sites enrolled a single cohort and the clinical data were used in two reading studies.

A. Study Inclusion/Exclusion Criteria for Both Reader Studies

1. Inclusion Criteria

Women over 40 years of age who were entering a participating facility for diagnostic mammography due to a recommendation for diagnostic mammography based on screening mammography results; palpable findings by clinical breast exam; skin thickening; spontaneous nipple discharge; or focal unilateral breast pain were included in the study.

2. Exclusion Criteria

Women who were under the age of 40, pregnant or suspicious of being pregnant; had breast implants; had breasts too large to be adequately positioned on 24x30 cm screen-film image receptor; had non-focal or bilateral breast pain; or who were unable or unwilling to understand or execute the patient consent form were excluded from the study.

Entry bias was minimized by entering all women attending for diagnostic mammography and willing to consent to the study by both Senographe 2000D and SFM. Entry bias was further minimized by imaging all women entering the study with both SFM and Senographe 2000D. Even if a woman entered the study because of a positive screening mammogram, a second SFM as well as a Senographe 2000D was taken to minimize any possibility of entry bias.

B. Study Population

Six hundred forty-one (641) patients were enrolled in the study at the four study sites. These women underwent both SFM and Senographe 2000D of one or both breasts.

To enrich the number of cancer cases in the study cohort, 21 additional cancer cases were obtained from a complementary study of Senographe 2000D currently being conducted at the University of Colorado Health Sciences Center (UCHSC) and University of Massachusetts Medical Center (UMMC) on a screening population using the GE-Senographe 2000D system (hereafter, "Army screening study").

Informed consent was obtained from 21 patients enrolled in the Army screening study. This provided 19 additional cancer cases for Reader Study #1 (11 from UCHSC and 8 from UMMC) and 20 additional cancer cases for Reader Study #2 (12 from UCHSC and 8 from UMMC) from a total of approximately 4,000 women screened by both SFM and Senographe 2000D in the Army screening study up to the end of 1998. One (1) patient, however, had to be excluded from both reader studies because her Senographe 2000D images were not available for interpretation in the study. A second case had to be excluded from Reader Study #1 because the additional informed consent had not been obtained at the time of the conclusion of the reader study.

1. Reader Study #1 Cohort

For Reader Study #1, 16 subjects (14 diagnostic study non-cancer cases and 2 UCHSC-UMMC screening study cancer cases) could not be included in the study analysis for the following reasons:

- 5 diagnostic cohort patients did not meet the inclusion/exclusion criteria.
- 11 cases (9 diagnostic cohort and 2 screening cohort cases) could not be included because their SFM images (5) or Senographe 2000D images (6) were not available for interpretation during the study (i.e., SFM films checked out for patient care, additional consent form for screening study patients not obtained prior to conclusion of the reader study, or lost films).

Excluding these 16 women brought the total number of patients who contributed both SFM and Senographe 2000D images to the Reader Study #1 to 646, 641 enrolled in the diagnostic study plus 21 screening study cancer cases minus 16 excluded cases. No additional selection of study participants occurred. These 646 women are referred to as the "Reader Study #1 cohort". The number of known cancers included in the Reader Study #1 cohort totaled 47 (28 cancer cases from the diagnostic cohort and 19 cancer cases from the Army screening study cohort). Of the 47 cancers, 22 were in the left breast, 25 were in the right breast. There were no known cases of bilateral breast cancer.

No serious adverse events occurred among the women in the study.

2. Reader Study #2 Cohort

The second reader study was performed on essentially the same set of acquired cases. The purpose of the second reader study was to reduce as many of the sources of variability as possible and to provide a balanced study design for efficient estimation of outcomes.

For Reader Study #2, 37 patients (32 non-cancer patients and 5 cancer patients) could not be included in the study analysis. The reasons for exclusion from the study analysis were as follows:

- 5 patients did not meet the inclusion/exclusion criteria.
- 13 patients could not be included because their SFM images (8) or Senographe 2000D images (5) were not available for interpretation during the study (i.e., SFM films checked out for patient care, lost films, etc.).
- 19 patients could not be included due to inconsistency in lesion markers between SFM and Senographe 2000D acquisitions.

Excluding these 37 cases brought the total number of patients who contributed both SFM and Senographe 2000D images to the Reader Study #2 to 625, 641 enrolled in the diagnostic study plus 21 Army screening study cancer cases minus 37 excluded cases. No additional selection of study participants occurred. These 625 women are referred to as the "Reader Study #2 cohort". The number of known cancers included in the Reader Study #2 cohort totaled 44 (24 cancer cases from the diagnostic cohort and 20 cancer cases from the screening cohort). Of the 44 cancers, 19 were in the left breast, 25 were in the right breast. There were no known cases of bilateral breast cancer.

No serious adverse events occurred among the women in the study.

C. Demographics

Table 1 describes the study cohort for Reader Study #1 and Reader Study #2 with respect to age, ethnicity, history of breast disease, and hormone replacement use.

Table 1: Age, Ethnicity, and History

		Study #1	Study #2
• Age Data:	Mean:	55	55
	Median:	56	53
	Range:	40-86	40-86
• Ethnicity:	White (non-Hispanic)	85%	87%
	African American	8%	6%
	Hispanic	2%	2%
	Asian	1%	1%
	Other	2%	2%
	Not reported	3%	3%
• Reported history of breast disease		34%	35%
• Reported history of hormone replacement therapy		33%	34%

IMAGE INTERPRETATION

A. Reader Study #1

In the first reader study, both screen-film and digital mammograms were independently interpreted for each case by at least two MQSA-qualified interpreting physicians. To minimize recall bias, an interval of at least 30 days between interpretations of the same case on the two different modalities was used. To ensure that interpreting physicians had no prior knowledge of each case, both SFM and Senographe 2000D images were interpreted by primary readers located at a different site than the site of image acquisition.

No prior films, patient histories or any other demographic information accompanied the interpretation of either modality. These reading conditions are similar to those encountered in a screening environment. Original screen-film images included the patient name; digital images did not include the patient name, nor did they include any other identifier that could be linked to the screen-film images. Each interpreting physician read approximately one-half of the screen-film mammograms first and approximately one-half of the digital mammograms first.

ACR BIRADS categories shown in Table 2 were used to assess findings for each modality.[1]

Table 2: ACR BIRADS Categories

ACR BIRADS Category	Finding
0	Needs further evaluation
1	Normal
2	Abnormal – benign
3	Abnormal – probably benign
4	Suspicious for cancer
5	Highly suspicious for cancer

ACR BIRADS categories 1 (normal), 2 (benign), and 3 (probably benign) with greater than 6 month follow-up were considered negative for breast cancer for both SFM and Senographe 2000D interpretations. ACR BIRADS categories 0 (needs further evaluation), 3 (probably benign) with less than or equal to 6 month follow-up, 4 (suspicious for cancer) and 5 (highly suspicious for cancer) were considered positive for breast cancer for both SFM and Senographe 2000D interpretations.

In an attempt to reduce interpretation variability, when the two independent primary interpretations for a given modality disagreed in terms of positive or negative for breast cancer, a third independent interpretation was performed by one of the secondary readers. The final interpretation for that modality

was that of the majority (2 out of 3). The same adjudication procedure was applied to each modality in cases where the primary readers for that modality disagreed. Reading of the second modality by each interpreting physician was spaced at least 30 days from the interpretation of the previous modality. If a third independent interpretation was required for both SFM and Senographe 2000D, those readings were also spaced at least 30 days apart. Data for both recall rates and sensitivities of the two modalities were analyzed comparing reader to reader (to eliminate inter-reader variability) and by comparing adjudicated (best 2 of 2 or 3) interpretations for each modality.

B. Reader Study #2

The purpose of the second reader study was to reduce as many sources of study variability as possible and to provide a balanced design for efficient estimation of outcomes. To reduce reader variability, five MQSA-qualified interpreting physicians each read all Senographe 2000D and all SFM images included in the study cohort. Analysis compared each reader's interpretation of Senographe 2000D to their own interpretation of SFM, so that inter-reader variability could be eliminated. Additional quality control measures were taken to ensure that lesion markers, when present, were identical in both Senographe 2000D and SFM images and the printing of Senographe 2000D images was adequate. All interpreting physicians participating in Reader Study #2 received uniform instructions, as described below.

The reading team for this reader study consisted of five MQSA-qualified radiologists. None of these interpreting physicians had any involvement in image acquisition or in Reader Study #1. Each interpreting physician independently read all SFM and all Senographe 2000D cases, separated by at least 30 days. Each interpreting physician read half of the SFM cases first and half of the Senographe 2000D cases first.

Both SFM and Senographe 2000D images were presented without any history data or marks on the mammograms to each the five readers in random order. No prior films, patient histories or any other demographic information accompanied the interpretation of either modality. These reading conditions are similar to those encountered in a screening environment. All five readers interpreted all films with each modality (separated by at least 30 days), a total of 1250 assessments per reader.

ACR BIRADS categories shown in Table 5 were used to assess findings for each modality.[1] ACR BIRADS categories 1 (normal) and 2 (benign) were considered negative for breast cancer for both SFM and Senographe 2000D interpretations. ACR BIRADS categories 0 (needs further evaluation), 3 (probably benign), 4 (suspicious for cancer) and 5 (highly suspicious for cancer) were considered positive for breast cancer for both SFM and Senographe 2000D interpretations. In an actual screening situation or a purely screening study, the use of the BIRADS 3 category is relatively uncommon.

C. Side-By-Side Feature Analysis Comparison Study

A side-by-side feature analysis comparison of lesions in Senographe 2000D and SFM images, was conducted again using hardcopy film output of Senographe 2000D images and original SFM films. This side-by-side feature analysis comparison included 40 cancer cases within the study population for which the previous reading study had been completed for all primary readers. Five experienced mammography radiologists (all of whom were primary readers in Reader Study #1) independently examined all films from each modality on these cases and ranked each view (MLO or CC) of each of the 40 cases in terms of 1) the conspicuity of cancers, 2) visibility (inclusion) of tissue at the chest wall, and 3) visibility of tissue at or near the skin line of the breast. Each criterion was scored for relative lesion conspicuity or tissue visibility between Senographe 2000D and SFM using an 11-point Likert scale. In addition, radiologists participating in the side-by-side analysis recorded the primary and, if relevant, the secondary signs of cancer for the four choices of calcifications, mass, focal asymmetry, or architectural distortion. Lesion conspicuity scores were analyzed separately for each lesion type.

STAGE AND SIZE DISTRIBUTION OF CANCERS IN THE STUDY COHORT

The distribution of cancer stages in the study cohort for the Reader Study #1 is listed in Table 3. The table is further broken down into the stage distribution of cancers in the diagnostic cohort and the stage distribution of cancers in the screening study cohort. The Agency for Health Care Policy and Research (AHCPR) Clinical Practice Guidelines #13: Quality Determinants of Mammography lists the marker of a good mammography program that at least 50% of detected cancers are Stage 0 and 1 cancers. The study group satisfies that requirement by having 58% of the total number of cancers in the stage 0 and 1 category.

Table 3: Stage Distribution of Cancers in Reader Study #1

Cancer Stage	0 In-Situ	I	II	III	IV	Total
Entire Study Cancer Cases	12 26%	15 32%	15 32%	3 6%	2 4%	47 100%
Diagnostic Cohort Cancer Cases	7 25%	8 29%	9 32%	3 11%	1 3%	28 100%
Screening Study Cancer Cases	5 26%	7 37%	6 32%	0 0%	1 3%	19 100%

Table 4 gives the size distribution of cancer cases in Reader Study #1. The AHCPR guidelines list the marker of a good mammography program that at least 30% of detected cancers are less than or equal to 1 cm in size. The entire study cohort for Reader Study #1 had 38% of cancers less than or equal to 1 cm in size.

Table 4: Size Distribution of Cancers in Reader Study #1

Tumor Size	All Patients (N=47)	Diagnostic Cohort Cancers Only (N=28)	Screening Cohort Cancers Only (N=19)
Number of Cancer Cases ≤1 cm	18 38%	8 29%	10 53%
Number of Cancer Cases > 1 cm	29 62%	20 71%	9 47%

The stage distribution of cancers in the study cohort for Reader Study #2 is listed in Table 5. The sum of Stage 0 and 1 cancers is 61%, well above the AHCPR guideline recommended limit of 50%.

Table 5: Stage Distribution of Cancers in Reader Study #2

Cancer Stage	0 In-Situ	I	II	III	IV	Total
Entire Study Cancer Cases	12 27%	15 34%	13 29%	2 5%	2 5%	44 100%
Diagnostic Cohort Cancer Cases	7 29%	7 29%	7 29%	2 8%	1 4%	24 100%
Screening Study Cancer Cases	5 25%	8 40%	6 30%	0 0%	1 5%	20 100%

Table 6 gives the size distribution of cancer cases in Reader Study #2, showing that the study distribution of minimal cancers (≤ 1 cm in size) of 43% is well within the AHCPR recommended limit of 30%.

Table 6: Size Distribution of Cancers in Reader Study #2

Tumor Size	All Patients (N=44)	Diagnostic Cohort Cancers Only (N=24)	Screening Study Cohort Only (N=20)
Number of Cancer Cases ≤1 cm	19 43%	8 33%	11 55%
Number of Cancer Cases > 1 cm	25 57%	16 67%	9 45%

The results, along with the absence of any case selection in the methods of accrual of study subjects, indicate that the subjects were representative of the general mammography population in the United States.

RESULTS AND DATA ANALYSES

Results are presented below for Reader Study #1, Reader Study #2, and the Side-by-Side Feature Analysis Study. Three separate analyses were performed for each reader study to evaluate the non-inferiority of Senographe 2000D to SFM. Those analyses were: comparison of recall rates for Senographe 2000D and SFM; a comparison of sensitivities of Senographe 2000D and SFM for cancers found in the cohort evaluated; and receiver operating characteristics (ROC) analysis.

A. Test 1: Recall Rate Comparison Data Analysis

A primary concern in the clinical use of Senographe 2000D is whether the modality results in a significant excess of false positives (patients recommended for additional imaging studies or for biopsy) compared to SFM. The entire study cohort and the non-cancer cohort were analyzed to compare recall rates using a paired comparison analysis of cases based on comparisons of overall recall rates and their Senographe 2000D and SFM final assessments. The determination of non-inferiority was based on the cases that disagreed concerning recall (i.e., the final interpretation using one modality was positive, the final interpretation using the other modality was negative).

1. Recall Rate Results – Reader Study #1

Primary interpretation recall rate results for SFM and Digital are provided in Table 7.

Table 7: Study #1 - Primary Interpretation Recall Rate Results

Reader A vs. Reader A Plus Reader B vs. Reader B

	All Cases	Non-Cancer Cases Only
Number of Readings of Each Modality	1,292	1198
Digital Recall Rate	45%	43%
Screen-film Recall Rate	47%	45%
p-value for Rejection of the Null Hypothesis	<0.001	<0.001

The recall rate test assumes a tolerable difference of $\delta = 0.05$ between the recall rate of Senographe 2000D and SFM (that is, that the recall rate of Senographe 2000D is not greater than 5% more than the recall rate of SFM). The observed results indicate that the recall rate of Senographe 2000D was lower than the recall rate of SFM. Moreover, the recall rate of Senographe 2000D was sufficiently lower than that of SFM (and the number of study participants was sufficiently large) to reject the

null hypothesis with a high degree of statistical significance ($p<0.001$), whether all cases or only non-cancer cases were considered.

These unadjusted combined p-values were confirmed by modeling the differences in recall rates using a generalization of the standard linear model. This enables the analysis of data generated from several sources of variation, multiple random effects and repeated measures. The estimation was made using the SAS/STAT PROC Mixed software[6]. The estimated mean difference between the recall rates was –1.78%, with a 95% confidence interval of [-5.66, 2.10]. The null hypothesis (digital recall rate greater by more than 5% than film-screen recall rate) can thus be rejected and the corresponding adjusted p-value is less than 0.001. The value of π was also estimated and tested using Generalized Estimating Equations (GEE models) with PRO GENMOD. The estimated value was 0.5322, with 0.4167 as the lower value of the 95% confidence interval. This result allows also to reject the null hypothesis and the corresponding adjusted p-value 0.029% is larger as the size of the sample is limited to the discordant pairs.

Table 8 shows the adjusted p-values for both models applied to all cases and non-cancer cases only. The null hypothesis can be rejected in all cases.

Table 8: Study #1 – Recall Rate Results Adjusted For Multiple Readers Reading Same Cases

	All Cases	Non-Cancer Cases Only
PROC MIXED Results		
Estimated Digital Recall Rate (Mean)	49.22%	47.13%
Estimated Screen-film Recall Rate (Mean)	51.00%	49.31%
Difference in Means (SE)	-1.78 (1.94)	-2.17 (2.01)
95% Confidence Intervals(CI)	[-5.66, 2.10]	[-6.11, 1.77]
To Reject Null Hypothesis the Difference in Means Must Be	<5%	<5%
Adjusted p-value for Rejection of the Null Hypothesis using PROC MIXED	<0.001	<0.001
PROC GENMOD Results		
Model Estimated □ value	0.5322	0.5241
Lower Bound of 95% CI for □	0.4167	0.4048
To Pass Recall Rate Test, □ Must Be ≥	0.40	0.40
Adjusted p-value for Rejection of the Null Hypothesis using GENMOD	0.0294	0.0433

Note: Test in PROC MIXED uses all observations. GENMOD uses only the discordant pairs, thus has a much smaller sample size.

2. Adjudicated Results for Recall Rate in Study #1

Comparing Senographe 2000D and SFM interpretations for adjudicated reading results for non-cancer cases only yields the results shown in Table 9.

Table 9: Study #1 - Adjudicated Mammography Recall Rate Results

Entire Cohort Included	All Cases	Non-Cancer Cases Only
Number of Readings of Each Modality	646	599
Digital Recall Rate	44%	41%
Screen-film Recall Rate	46%	42%
p-value for Rejection of the Null Hypothesis	<0.001	<0.001

The recall rate test again assumes a tolerable difference of $\delta = 0.05$ between the recall rate of Senographe 2000D and SFM (that is, that the recall rate of Senographe 2000D is not more than 5% greater than the recall rate of SFM). The observed results based on adjudicated readings indicate that the recall rate of Senographe 2000D is lower than the recall rate of SFM. Moreover, the recall rate of Senographe 2000D is sufficiently lower than that of SFM (and the number of study participants is sufficiently large) to reject the null hypothesis with a high degree of statistical significance ($p<0.001$), whether the adjudicated readings for all cases or only non-cancer cases are considered.

The recall rate test results indicate, with a high degree of statistical confidence, that Senographe 2000D does not recall a higher proportion of women than SFM. This conclusion holds whether we compare primary reader interpretations of the two modalities (which includes only intra-reader variability along with possible positioning and modality differences) or adjudicated interpretations of the two modalities (which also includes inter-reader variability).

3. Reader Study #2 Recall Rate Results

The recall rate comparison for Reader Study #2 used the same null hypothesis and the same methods of comparison as that given above for Reader Study #1. Comparing Senographe 2000D and SFM interpretations by readers for all cases, and for non-cancer cases only, yields the results in Table 10.

Table 10: Study #2 - Interpretation Recall Rate Results

	All Cases	Non-Cancer Cases Only
Number of Readings of Each Modality	3125	2905
Digital Recall Rate	47%	45%
Screen-film Recall Rate	49%	47%
Unadjusted p-value for Rejection of the Null Hypothesis	<0.001	<0.001

The recall rate test assumes a tolerable difference of $\delta = 0.05$ between the recall rate of Senographe 2000D and SFM (that is, that the recall rate of Senographe 2000D is not greater than 5% more than the recall rate of SFM). The observed results indicate that the recall rate of Senographe 2000D was lower than the recall rate of SFM. Moreover, the recall rate of Senographe 2000D was sufficiently lower than that of SFM (and the number of study participants was sufficiently large) to reject the

null hypothesis with a high degree of statistical significance (unadjusted p<0.001), whether all cases or only non-cancer cases were considered.

These unadjusted combined p-values were confirmed using a generalized linear model PROC MIXED and Table 11shows the adjusted p-values (adjusted for multiple readers reading the same cases) obtained by modeling the differences in recall rates using a generalization of the standard linear model as previously described in the Study #1. This enables the analysis of data generated from several sources of variation, multiple random effects and repeated measures.

Table 11: Study #2 – Recall Rate Results Adjusted for Multiple Readers Reading Same Cases

	All Cases	Non-Cancer Cases Only
PROC MIXED Results		
Estimated Digital Recall Rate (Mean)	46.98%	45.37%
Estimated Screen-film Recall Rate (Mean)	48.83%	47.26%
Difference in Means (SE) 95% Confidence Intervals(CI)	1.86 (1.22) [-4.25, 0.54]	1.89 (1.26) [-4.36, 0.58]
To Reject Null Hypothesis the Difference in Means Must Be	<5%	<5%
Adjusted p-value for Rejection of the Null Hypothesis using PROC MIXED	<0.001	<0.001
PROC GENMOD Results		
Model Estimated □ value Lower Bound of 95% CI for □	0.6737 0.4164	0.4782 0.4200
To Pass Recall Rate Test, □ Must Be ≥	0.412	0.411
Adjusted p-value for Rejection of the Null Hypothesis using GENMOD	0.0382	0.0286

Note: Test in PROC MIXED uses all observations. GENMOD uses only the discordant pairs, thus has a much smaller sample size.

The difference in means of recall rates = 1.86 with a corresponding 95% confidence interval [-4.25, 0.54] allows rejection of the null hypothesis with an adjusted p-value <0.001. Similarly, the lower bound of 5% confidence interval for π is estimated to be 0.4164 which allows rejection of the null hypothesis with an adjusted p-value = 0.0382.

B. Test 2: Sensitivity Comparison

Every effort was made to determine breast cancers occurring among the study cohort, by obtaining biopsy results in all cases going to biopsy and through follow-up at each acquisition site. All confirmed breast cancers found by any methods among the study cohort were used in this analysis. A comparison was made of the fraction of total cancers among the study cohort that were detected by Senographe 2000D and SFM, giving an estimated sensitivity for each modality. The fraction of cases correctly classified by a modality (true positives among the cancer cases by that modality divided by all known cancers) was compared using an exact binomial calculation, taking into account the fact that the true positive fractions were correlated.

The null hypothesis was that Senographe 2000D was inferior to SFM in terms of sensitivity by having a true positive fraction at least 10% lower than that of SFM. The rejection of the null hypothesis would provide further evidence for the non-inferiority of Senographe 2000D.

1. Sensitivity Results – Study #1

Comparing Senographe 2000D and SFM interpretations in terms of sensitivity to breast cancer, both by primary reader interpretations and by adjudicated readings, using the cancer case data yields the results in Table 12:

Table 12: Study #1 - Modality Sensitivity Results

Cancer Case Readings Only	A vs. A + B vs. B	Adjudicated Readings
Number of Readings of Each Modality	94	47
Senographe 2000D Sensitivity	78%	85%
SFM Sensitivity	74%	85%
p-value for Rejection of the Null Hypothesis	<0.01	= 0.062

The alternative hypothesis of Senographe 2000D not having a significantly lower sensitivity than SFM assumed a tolerable difference of $\delta = 0.10$. In that case, the alternative hypothesis stated above would be supported by $\pi \geq 0.28$ for comparing primary readings and $\pi \geq 0.21$ for adjudicated readings.

The results stated above for primary readings yielded $\pi = b/(b+c) = 13/(13+10) = 0.57$, which is consistent with the non-inferiority of Senographe 2000D in terms of sensitivity. This yielded a measured sensitivity of 78% for Senographe 2000D and 74% for SFM, supporting the claim that Senographe 2000D does not have a significantly lower sensitivity to breast cancer than SFM.

Statistical analysis of these measured results showed that primary readings are consistent with rejection of the null hypothesis (that Senographe 2000D has a lower sensitivity to breast cancer than SFM) with an unadjusted p-value of less than 0.01. Modeling the difference between the sensitivities led to a mean value of 3.19 with a 95% confidence interval: [-8.94, 15.32] which allows to reject the null hypothesis with an adjusted p-value = 0.0166. Generalized estimating equation models for π were unable to converge and estimate the off-diagonal elements due to the reasonably high agreement between the modalities by observer. For Reader A1, there were only 6 of 17 cancers discordant. For Reader B1 there were 2, for Reader C1 there were 7, for Reader D1 there were 4, and for Reader E1 there were 3 discordant cancers. Three of the readers found more cancers with Senographe 2000D and two found more with SFM.

Table 13 shows the estimated 3% difference in sensitivity for Senographe 2000D and a p-value of 0.0166 for the rejection of the inferiority of Senographe 2000D by 10% or more.

Table 13: Study #1 - Sensitivity Results Adjusted For Multiple Readers Reading Same Cases

	Estimated Sensitivity
PROC MIXED Results	
Estimated Senographe 2000D Sensitivity (Mean)	77.44%
Estimated SFM Sensitivity (Mean)	74.25%
Difference in Means (SE) 95% Confidence Intervals(CI)	3.19 (6.19) [-8.94, 15.32]
To Reject Null Hypothesis the Difference in Means Must Be	> -10%
Adjusted p-Value for Rejection of the Null Hypothesis using PROC MIXED	0.0166
PROC GENMOD Results	
Adjusted p-value for Rejection of the Null Hypothesis using GENMOD was not estimable due to small sample size on off-diagonal elements	

Note: Test in PROC MIXED uses all observations. GENMOD uses only the discordant pairs, thus has a much smaller sample size.

2. Adjudicated Results for Sensitivity – Study #1

Within our study cohort using adjudicated readings, the measured sensitivity of both Senographe 2000D and SFM was 85%, supporting the claim that Senographe 2000D does not have a significantly lower sensitivity to breast cancer than SFM. Statistical analysis of these adjudicated results showed that they are consistent with rejection of the null hypothesis (that Senographe 2000D has a lower sensitivity to breast cancer than SFM) with a p-value of 0.062. The small number of discordant breast cancers with adjudicated interpretations (a total of 8), means that there are only 9 possibilities for the discordant cases, summarized in Table 14 below. The table gives the p-values for each discrete possibility for b and c among 8 discordant cases, indicating that the p-values jump from 0.013 for 5 out of 8 correctly called positive by digital to 0.062 for 4 out of 8 correctly called positive by digital, to 0.23 for 3 correctly called positive by digital. Thus, a p-value of 0.062 with only 8 discordant findings is consistent with rejection of the null hypothesis (that Senographe 2000D has a lower sensitivity in detecting breast cancer than SFM).

Table14: Discrete p-values with 8 Discordant Cancer Cases

b	C	p-value
8	0	---
7	1	.00012
6	2	.0016
5	3	.013
4	4	.062
3	5	.23
2	6	.53
1	7	.85
0	8	1.0

Restricting the sensitivity comparison in Reader Study #1 to Stage 0 and 1 cancers (Table 3), Senographe 2000D had a sensitivity of 85% compared to 74% for SFM. Restricting the comparison of sensitivity to minimal cancers ($\leq$ 1 cm is maximum size) (Table 4), Senographe 2000D had a sensitivity of 83% compared to a sensitivity of 70% for SFM. These results indicate that Senographe 2000D was not shown to have equal sensitivity to SFM based on the detection of larger, later stage cancers; Senographe 2000D had higher sensitivity than SFM in the detection of smaller, earlier stage cancers.

3. Sensitivity Comparison Results Study #2

The sensitivity comparison for Reader Study #2 used the same null hypothesis and the same method of comparison as that given above for Reader Study #1. Comparing Senographe 2000D and SFM interpretations in terms of sensitivity to breast cancer using the cancer case data yields the results shown in Table 15.

Table 15: Study #2 - Modality Sensitivity Results

Cancer Case Readings Only	
Number of Readings of Each Modality	220
Senographe 2000D Sensitivity	68%
SFM Sensitivity	70%
Unadjusted p-value for Rejection of the Null Hypothesis	0.006

The alternative hypothesis of Senographe 2000D not having a significantly lower sensitivity than SFM assumed a tolerable difference of $\delta = 0.10$. In that case, the alternative hypothesis stated above would be supported by $\pi \geq 0.331$. The results stated above for primary readings yielded $\pi = b/(b+c) = 31/(31+34) = 0.477$, which is consistent with the non-inferiority of Senographe 2000D in terms of sensitivity. This yielded a measured sensitivity of 68% for Senographe 2000D and 70% for SFM, supporting the claim that Senographe 2000D does not have a significantly lower sensitivity to breast cancer than SFM.

These unadjusted combined p-values were confirmed using a generalized linear model using PROC MIXED and PROC GENMOD available in the SAS/STAT Software package. These models enable the adjustment for reader and subjects, while estimating the off diagonal (non-concordant) results.

Table 16 shows the estimated sensitivities and 2-sided confidence intervals for the difference in sensitivity.

Table 16: Study #2 - Sensitivity Results Adjusted For Multiple Readers Reading Same Cases

	Estimated Sensitivity
PROC MIXED Results	
Estimated Senographe 2000D Sensitivity (Mean)	68.18%
Estimated SFM Sensitivity (Mean)	69.55%
Difference in Means (SE) 95% Confidence Intervals(CI)	-1.36 (4.39) [-9.96, 7.24]
To Reject Null Hypothesis the Difference in Means Must Be	> -10%
Adjusted p-Value for Rejection of the Null Hypothesis using PROC MIXED	0.0245
PROC GENMOD Results	
Model Estimated □ value Lower Bound of 95% CI for π	0.4636 0.2994
To Pass Alternative Hypothesis Sensitivity Criterion, π Must Be Greater Than:	0.331
Adjusted p-value for Rejection of the Null Hypothesis using GENMOD	0.0963

Note: Test in PROC MIXED uses all observations. GENMOD uses only the discordant pairs, thus has a much smaller sample size.

It is important to emphasize that the PROC MIXED test uses all observations. GENMOD uses only discordant pairs. In this particular study, the number of discordant pairs was very low. Thus, the GENMOD analysis has a much smaller sample size. More importantly, the PROC MIXED had a larger sample size and thus led to more statistically meaningful results. The difference in means of sensitivities: -1.36 with a corresponding 95% confidence interval [-9.96, 7.24] allows rejection of the null hypothesis with an adjusted p-value = 0.0245. The estimated value for π is 0.4636, with a lower bound of the 95% confidence interval equal to 0.2994. This value is not sufficient to reject the null hypothesis. This result is driven by the reduction of the sample size.

Considering ACR BIRADS category 3 cases as negative shifts the SFM call of one reader's assessment of one case from positive to negative, lowering the overall sensitivity of SFM to 69%, compared to 68% for Senographe 2000D. None of the statistical analysis conclusions with regard to sensitivity are changed by shifting BIRADS category 3 cases from positive to negative.

Restricting the sensitivity comparison in Reader Study #2 to Stage 0 and 1 cancers (Table 5), Senographe 2000D had a sensitivity of 65% compared to 64% for SFM. Restricting the comparison of sensitivity to minimal cancers ($\leq$ 1 cm is maximum size) (Table 6), Senographe 2000D had a sensitivity of 63% compared to 57% for SFM. These results indicate that Senographe 2000D was not shown equal in sensitivity to SFM based on the detection of larger, later stage cancers. Senographe 2000D had slightly higher sensitivity than SFM in the detection of smaller, earlier stage cancers.

C. Test 3: ROC Analysis

The independent interpretation of Senographe 2000D and SFM, along with the collection of probabilities of cancer from each interpretation given a BIRADS code of 0, 3, 4 or 5 (on a 0-100% scale), allowed the construction of ROC curves for each modality.

ROC curves have been constructed using probabilities of cancer based on Hanley-McNeil ROC analysis methods[2,3] under three different conditions: for all individual primary readers in the study (other than one primary reader who interpreted only 9 non-cancer cases), the collective results for all primary readers for each case, and for adjudicated readings based on the mean probability of cancer for the two readers making the adjudicated decision.

Since a probability of cancer was estimated for each breast, for all patients having both breasts imaged, the maximum probability of the two non-cancer breasts was used; for breasts with cancer, the probability of breast cancer specific to the breast with cancer was used. The ROC curves for each case, along with the integrated areas under the ROC curves using the Hanley-McNeil method (which is consistent with a linear interpolation between ROC data points and usually results in areas lower than the binormal ROC curves because fewer assumptions are made) are presented below.

1. ROC Results – Study #1

Figure 7 shows ROC results combining all initial readings (corresponding to A vs. A plus B vs. B, where A and B represent the two primary readers of Senographe 2000D and SFM for each case, regardless of the actual reader). Figure 8 shows ROC results for the adjudicated readings, averaging the probabilities of cancer for the two readers that determined the adjudicated result (positive or negative). ROC curves based on BIRADS categories rather than probabilities of cancer gave similar results.

Figure 7: ROC Results for All Primary Readers Combined in Reader Study #1

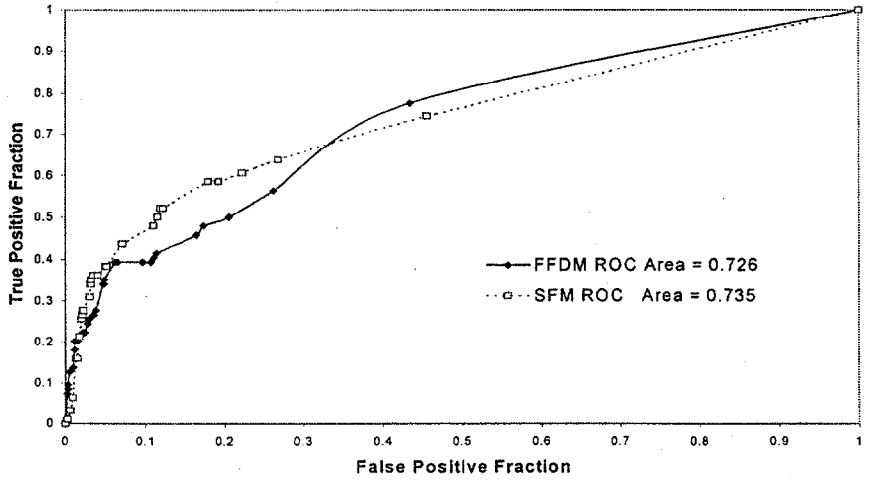
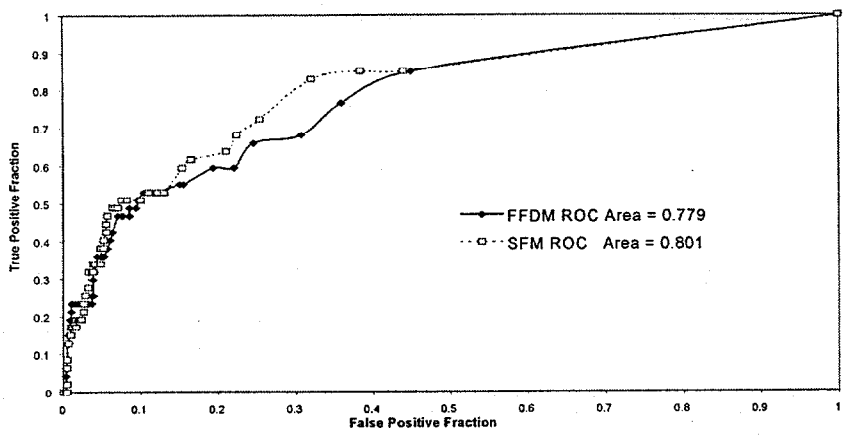


Figure 8: Adjudicated ROC Results in Reader Study#1



The null hypothesis for ROC areas is analogous to the null hypothesis for recall rate and sensitivity test. The null hypothesis is that the ROC area for Senographe 2000D is significantly lower than the ROC area of SFM (by more than 0.10). In each case in which collective ROC analysis results were compared for the two modalities, the alternative hypothesis was easily met. Moreover, in each case of collective ROC analysis, statistical tests based on a z-statistic indicated that the null hypothesis could be rejected with reasonable statistical significance. These ROC analysis results and the p-values associated with rejection of the null hypothesis in each case are summarized in Table 17.

Table 17: Study #1 - Summary of ROC Results and Associated p-values

ROC Curve Comparison	A_{SFM}	$A_{Senographe\ 2000D}$	SE_{SFM}	$SE_{Senographe\ 2000D}$	Adjusted Correlation r	p-value
All primary readings Combined	0.735	0.726	0.032	0.030	0.49	0.0015
Adjudicated readings, taking mean cancer probability of readers	0.801	0.779	0.037	0.038	0.52	0.017

Notes: SE_{SFM} = standard error of the SFM ROC curve area
$SE_{Senographe\ 2000D}$ = standard error of the Senographe 2000D ROC curve area
r = the correlation between ROC curve areas for Senographe 2000D and SFM (ref: Hanley and McNeil)[2,3]

Recognizing that there are correlated observations in the case of all primary readings combined, an attempt was made to analyze for the distinction between ROC curves that accounts for the overlap in cases interpreted. In this first study, the concern for potential bias or additional information constrained the design of the readings (i.e., each reader did not read the same cases). This led to overlap in cases read that was unbalanced among readers. To attempt to estimate an adjusted standard error of the area under the ROC curve adjusted for some correlation, we created a dataset of first readers and second readers. Using this dataset, we performed an ROC Analysis using the Multi-Reader, Multiple Case Software LABMRMC available from the University of Chicago. The results from this analysis are shown in Table18.

Table 18: Study #1 - Summary of ROC Results

ROC Curve Comparison	A_{SFM}	$A_{Senographe\ 2000D}$	SE_{SFM}	$SE_{Senographe\ 2000D}$	Mean Difference (95% Confidence Interval)
First Reader	0.774	0.771	0.043	0.041	Mean=0.004 (SE=0.0538) 95% CI= [-0.1017,0.1096]
Second Reader	0.705	0.693	0.050	0.048	Mean=0.012 (SE=0.0419) 95% CI= [-0.0699,0.0946]
Estimated Difference	0.741	0.733	0.049	0.047	Mean=0.0082 (0.0362)
Confidence Interval					95% CI=[-0.0629, 0.0792]

Notes: SE_{SFM} = standard error of the SFM ROC curve area
$SE_{Senographe\ 2000D}$ = standard error of the Senographe 2000D ROC curve area

The lower bound of the one sided confidence interval for testing the null hypothesis is -0.0513 significantly rejecting the inferiority hypothesis ($p<.003$).

These ROC results indicate that collective ROC curve areas are similar for the two modalities regardless of the method of analysis. Senographe 2000D had ROC curve areas well within 0.1 of SFM areas for all composite results. Analysis of the statistical significance of differences between ROC curve areas demonstrated that the null hypothesis could be rejected with statistical power (at least $p< 0.02$) in each case. Thus, ROC analysis results support the conclusion that Senographe 2000D is not inferior to SFM in the detection of breast cancer.

2. ROC Results – Study #2

ROC curves for Reader Study #2 have been constructed using probabilities of cancer (on a 0-100% scale) based on Hanley-McNeil ROC analysis methods[2,3]: for all individual readers in the study, and the collective results for all readers for each case.

Since a probability of cancer was estimated for each breast, this ROC analysis included each breast as a "case". Therefore, 44 "cases" had cancer and 953 "cases" (non-cancerous breasts) were without cancer. The ROC curves for all 5 readers combined are presented in Figure 3.

Figure 9: ROC Curves for All 5 Readers Combined in Reader Study #2

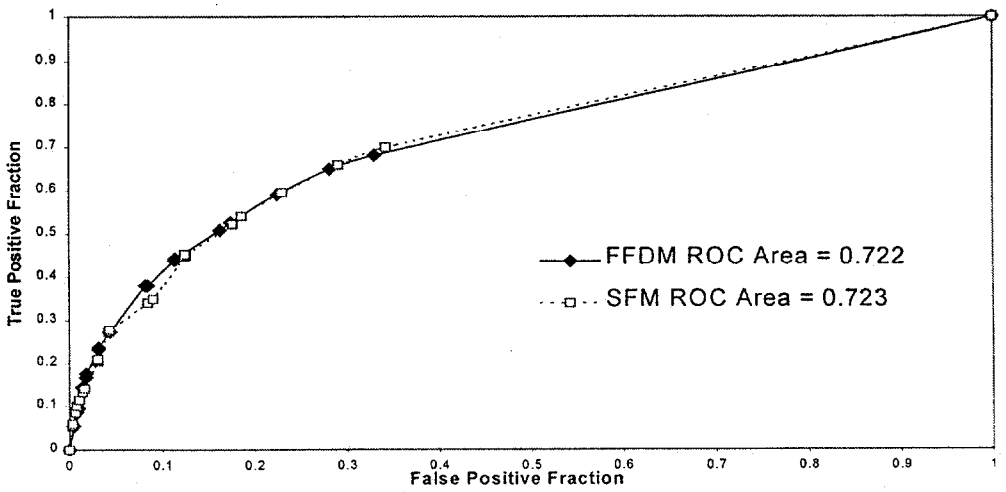


Table 19 summarizes ROC curve area results for each reader and all readers combined.

Table 19: Study #2 - Summary of ROC Analyses by Reader and For All Readers Combined and Associated P-values

Reader	A_z Senographe 2000D	A_z SFM	$SE_{Senographe\ 2000D}$ On A_z	$SE_{Senographe\ 2000D}$ On A_z	Adjusted Correlation (Hanley, McNeil)	H_0: Inferiority P-Value
A2	.729	.685	.044	.047	0.60	0.0002
B2	.720	.771	.046	.042	0.51	0.132
C2	.729	.768	.045	.041	0.56	0.066
D2	.720	.738	.046	.047	0.46	0.043
E2	.729	.708	.046	.047	0.62	0.0014
Total	.722	.723	.020	.020	.56	(unadjusted) <0.0001

The null hypothesis for ROC areas is analogous to the null hypothesis for recall rate and sensitivity test. The null hypothesis is that the ROC area for Senographe 2000D is significantly lower than the ROC area of SFM (by more than 0.1). The p-values listed in the last column of Table 20 indicate the confidence level for rejection of the null hypothesis. Rejection of the null hypothesis was indicated with three of the five individual readers and by the combined results of all 5 readers with high statistical significance (unadjusted $p<0.0001$).

3. Study #2 – ROC Curves Adjusted for Correlation of Observations

Recognizing that there are correlated observations, we analyzed ROC curves accounting for the overlap in patients and estimated a standard error of the area under the ROC curve adjusted for this correlation. We performed these ROC analyses using the Multi-Reader, Multiple Case Software LABMRMC available from the University of Chicago. We utilized all readings (breast by breast) and have checked the independence of the results by breast. There was virtually no correlation between the probability of cancer between the breast. In each modality-reader combination, the correlation never exceeded 0.06 and was generally 0.03 or lower. The effect of including all breasts was also checked by randomly selecting one breast per women (except when a cancer was present) and these results were virtually identical to those with the breast by breast analysis. This is likely due to the fact that the majority of breasts utilized had concordant probabilities of cancer of zero. Thus, a breast by breast analysis is reported. The results from this analysis are shown in Table 20.

Table 20: Study #2 - Summary of ROC Results and Associated p-values

ROC Curve Comparison	A_{SFM}	$A_{Senographe\ 2000D}$	SE_{SFM}	$SE_{Senographe\ 2000D}$	Mean Difference (95% Confidence Interval)
Reader #A2	0.785	0.797	0.043	0.042	Mean=-.011 (SE=.0469) 95% CI= (-0.1032,0.0809)
Reader #B2	0.686	0.739	0.051	0.043	Mean=-.053 (SE=.0502) 95% CI= (-0.1517,0.0454)
Reader #C2	0.756	0.756	0.057	0.056	Mean=-.000 (SE=.0646) 95% CI= (-0.1268,0.1266)
Reader #D2	0.794	0.749	0.037	0.048	Mean=0.047 (SE=.0588) 95% CI= (-0.0686,0.1621)
Reader #E2	0.796	0.731	0.040	0.053	Mean=0.063 (SE=0.0623) 95% CI= (-0.0592,0.1853)
Overall Results	0.767	0.758	0.0368	0.0344	Mean=0.009 (0.0324)
Confidence Interval					95% CI=(-0.0545, 0.0727)

Notes: SE_{SFM} = standard error of the SFM ROC curve area
$SE_{Senographe\ 2000D}$ = standard error of the Senographe 2000D ROC curve area

These ROC results indicate that collective ROC curve areas are within 0.01 of each other for the two modalities. Senographe 2000D had ROC curve areas well within 0.1 of SFM areas for composite results. Analysis of the statistical significance of differences between ROC curve areas demonstrated that the null hypothesis could be rejected and the confidence interval for the difference in areas shows that the ROC curve areas of the two modalities are not different. Thus, ROC analysis results support the conclusion that Senographe 2000D is not inferior to SFM in the detection of breast cancer.

C. Side-by-Side Feature Analysis

The criterion for case inclusion in the side-by-side analysis was all cancer cases for which all primary readings had been completed by the time of the side-by-side analysis. This criterion was used to prevent the possibility that readers in the first reader study might see a case in the side-by-side analysis and then be asked to perform an independent interpretation on that case later for the recall rate/sensitivity study. Therefore, 40 cancer cases of the total 47 identified in the study cohort were used for the side-by-side comparison. All comparisons involved original SFM (except for two cases for which only copy films of the SFM were available) and Senographe 2000D images printed on film.

All 40 cases had MLO comparisons of Senographe 2000D and SFM and 39 had CC comparisons (one case had an exaggerated CC supplied on SFM instead of a routine CC, so the CC comparison was eliminated prior to scoring by reviewers). This resulted in 40 MLO views and 39 CC views, or a total of 79 views, that were each scored independently by each of the 5 primary readers.

All side-by-side comparisons were performed by placing both SFM and Senographe 2000D on the same mammography alternator or bank of viewboxes. Film masking was used for each comparison. A mammography hot light was available at each reading station for each reader. Each case was scored independently by 5 board-certified, MQSA-qualified radiologists. Prior to the side-by-side comparison, the cancerous area was marked in each view on each modality. Each radiologist was asked to note the type of finding, including all that applied, selecting from the following list: mass, calcifications, architectural distortion, and focal asymmetry. Each view (MLO and CC) was compared separately using three different evaluation criteria: lesion conspicuity, inclusion of tissue along the chest wall, and visibility of tissue at or near the skin line of the breast.

The analysis was done by averaging the score in each of the three categories across readers for all views (5 readers x 79 views = 395 scores). An overall mean value was calculated across all readers and views. Scores for each reader were averaged across all views, giving a mean value for that reader. Scores for each view were averaged across all readers giving a mean value for that view. Table 21shows the overall mean and the range of mean values for readers and for views.

The average score for lesion conspicuity, S_C, was used to represent the lesion conspicuity result. As stated in the study protocol, the null hypothesis was that the average score S_C, averaged over all cancer cases for the 5 readers, is significantly worse for Senographe 2000D than for SFM.

H_o: $S_C > 6$, implying that visibility is significantly inferior on Senographe 2000D

The alternative hypothesis was:

H_a: $S_C \leq 6$, implying non-inferiority of Senographe 2000D.

The results of the side-by-side analysis are shown in Table 21. The overall mean is averaged over all readers and all views. The mean range by reader shows the range of mean scores across the five readers, averaged over all cases and views for each reader. The mean range by view shows the range of mean scores across all views, averaged over the five readers. The test requirement was that the overall mean score in each test category be less than 6.0.

Table 21: Summary of Side-by-Side Feature Analysis

Test	Overall Mean	Mean Range (by Reader)	Mean Range (by View)	Meets Test Requirement?
Lesion Conspicuity	5.17	4.91-5.34	0-9.8	Yes
Tissue Visibility at Chest Wall	5.21	4.80-5.42	3.4-8.4	Yes
Tissue Visibility at Skin Line	2.95	0.39-4.30	1.7-5.2	Yes

The mean score for lesion conspicuity, $S_C = 5.17$, reflects the non-inferiority of Senographe 2000D for lesion conspicuity and the ability to detect low-contrast lesions. Averaged over all 79 views, the range of S_C for the 5 readers was 4.91 to 5.34. Averaged over all five readers, the range of S_C for the 79 cancer case views was 0 to 9.8. T-tests indicate that the mean lesion conspicuity score of 5.17 is consistent with rejection of the null hypothesis (that $S_C > 6$) with a high degree of statistical significance ($p < .007$).

The mean score for visibility of tissue at the chest wall, $S_{CW} = 5.21$, reflects the non-inferiority of Senographe 2000D for inclusion of tissue at the chest wall. Averaged over the 79 views, the range of S_{CW} for the 5 consistent readers was from 4.80 to 5.42. Averaged over the 5 readers, the range of S_{CW} for the 79 views was 3.4 to 8.4. T-tests indicate that the mean chest wall visibility score of 5.21 is consistent with rejection of the null hypothesis (that $S_{CW} > 6$) with a high degree of statistical significance ($p < .001$).

SAS PRO mixed was again utilized to adjust for multiple readers assessing the same cases. The results are confirmed by this analysis, not only overall but for each radiologist separately.

The mean score for tissue visibility at the skin line of the breast was $S_{SL} = 2.95$, reflecting the non-inferiority of Senographe 2000D for inclusion of tissue at the skin line. This score in favor of Senographe 2000D was due to the use of a thickness equalization algorithm applied to all images of all cases included in the recall-rate, sensitivity, and side-by-side comparisons. Averaged over the 79 cases, the range of S_{CW} for the 5 readers was from 0.39 To 4.30. Averaged over the five readers, the range of S_{CW} for the 79 views was 1.7 to 5.2. T-tests indicate that the mean skin line visibility score of 2.95 is consistent with rejection of the null hypothesis (that $S_{SL} > 6$) with a high degree of statistical significance ($p < 0.00001$).

Table 22 summarizes mean lesion conspicuity scores and the score range (across views, averaged over the 5 readers) for each specific lesion type. The five interpreting physicians performing the side-by-side analysis were asked to specify the primary and secondary indicators of the lesion from the four categories listed in Table 22. The total number of views listed exceeds 79 because of multiple listings of lesion type for some cancers. The score range (averaged over all 5 reviewers) for each lesion type indicates that reviewers used a wide range of lesion conspicuity scores in each lesion category. The mean lesion conspicuity scores, however, are similar to the overall mean lesion conspicuity score of 5.17. There is no trend toward a particular lesion type having lower conspicuity on Senographe 2000D than on SFM.

Table 22: Summary of Side-by-Side Lesion Conspicuity for Specific Lesion Types Within the 40 Cancer Cases

Lesion Type	Number of Views	Reader Score	
		Mean	Range
Calcifications Present	42	5.21	0-8.0
Masses Present	53	5.17	1.8-9.8
Architectural Distortion Present	34	5.24	1.8-9.8
Focal Asymmetry Present	27	5.26	3.2-9.8
Calcifications Primary	24	5.33	0-8.0
Masses Primary	51	5.10	1.8-9.8
Architectural Distortion Primary	4	5.05	4.2-6.2

Note: No cases listed focal asymmetry as the primary lesion type.

These results demonstrate that Senographe 2000D is substantially equivalent (i.e., non-inferior) to SFM in lesion conspicuity, chest wall visibility, and visibility of tissue at the skin line.

STUDY CONCLUSIONS

Three different reader studies have been conducted to test the non-inferiority of Senographe 2000D relative to SFM. Two reader studies were analyzed to compare ROC results, sensitivities, and recall rates for the two modalities. A side-by-side feature analysis was performed to compare lesion conspicuity (including analysis of conspicuity for specific lesion types), visibility of tissue at the chest wall, and visibility of tissue at the skin line.

The following are the study results:

- The ROC curve areas for the Senographe 2000D and SFM systems are virtually identical.
- The sensitivity analysis demonstrated that the Senographe 2000D has a sensitivity comparable to that of SFM in the screening and detection of breast cancer.
- The specificity analysis demonstrated that the Senographe 2000D system results in fewer women being recalled than SFM.
- The side-by-side feature comparison data demonstrated that the Senographe 2000D system allows better visibility of tissue at the skin line than SFM and that the Senographe 2000D system is comparable to SFM for lesion conspicuity and visibility of tissue at the chest wall.

XI. CONCLUSIONS DRAWN FROM NONCLINICAL AND CLINICAL STUDIES

The results of the nonclinical and clinical studies conducted by the sponsor and described above provide a reasonable assurance of the safety and effectiveness of GE Medical Systems' full-field digital mammography for screening and diagnostic breast imaging. These findings therefore support FDA approval of the GE Senographe 2000D Full-Field Digital Mammography system for clinical use in screening and diagnostic mammography.

XII. PANEL RECOMMENDATION

A meeting of the FDA Radiological Devices Panel took place on December 16, 1999 to review the sponsor's submission, PMA P990066, as amended. The panel voted for approval and made the following recommendations:

1) The sponsor should deploy a soft copy workstation to serve as an adjunct to hard copy.
2) FDA should expedite approval of the soft copy modality.
3) Amend the labeling to include an executive summary section in the front of the labeling that emphasizes the difference between the study population and true screening and diagnostic populations.

The sponsor responded with revised labeling to meet condition 3) above. The other two conditions, 1) and 2), are advice to the sponsor and to FDA and will be considered.

XIII. FDA DECISION

CDRH concurred with the Radiological Devices Panel recommendation of December 16, 1999. The applicant's manufacturing facility was inspected on December 6-9, 1999 and was found to be in compliance with the Quality System regulations. FDA issued an approval order on January 28, 2000.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the attached labeling

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. Until such time as an FDA approved accreditation process for full-field digital mammography has been developed the Senographe 2000D Full Field Digital Mammography System must only be sold to screen-film accredited/certified facilities. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the attached labeling.

LABELING

Senographe 2000D Full Field Digital Mammography System
Information for Use

CAUTION: United States Federal law restricts this device to use by or on the order of a physician.

DEVICE DESCRIPTION

The Senographe 2000D has been designed to perform screening examinations as well as diagnostic views (including spot compression, magnified, and/or coned views). It is a modular system that eliminates the need for film cassettes and takes advantage of digital technology, including on-screen image display, networking, filming, and archiving.

The Senographe 2000D is equipped with a dual track X-ray tube (molybdenum/rhodium) and a digital detector. The digital detector is a flat panel of amorphous silicon on which cesium iodide is deposited to maximize detection of X-rays. Positioning operations and X-ray exposure are controlled by the Control Panel which also controls power to all parts of the Senographe 2000D system. The Senographe 2000D includes an acquisition work station ("AWS") monitor, keyboard and mouse, computer, electronics, accessory storage, and uninterruptible power supply. The AWS is used for image acquisition, processing, and display. The AWS can also be used for database management, and can send images to archive, review, or filming.

Several options are available for use with the Senographe 2000D system. These options include a Senographe 2000D review workstation (not to be used for final interpretation of examinations), a mass archiving system, a laser camera, networking capabilities, and CD-ROM interchange media. The Senographe 2000D review workstation is a stand-alone workstation with its own dedicated computer and image database. The review workstation supports image display, and manipulation.

INDICATIONS FOR USE

The Senographe 2000D system generates digital mammographic images that can be used for screening and in the diagnosis of breast cancer. The Senographe 2000D is intended to be used in the same clinical applications as traditional mammographic screen-film systems.

CONTRAINDICATIONS

There are no known contraindications.

WARNINGS and PRECAUTIONS

For User

Senographe 2000D

- For U.S. only, until such time as an FDA approved accreditation process for full-field digital mammography has been developed, the Senographe 2000D Full Field Digital Mammography System must only be used in MQSA screen-film accredited/certified facilities.

- The light box (on the AWS cart) must *not* be used for final interpretation of examinations. The ambient light conditions in the examination room, and the resulting light level of the light box, are incompatible with its use for final interpretations.

- The (AWS) workstation monitor must *not* be used for final interpretation of examinations. It is set up for optimum visualization with an ambient light level of 50 lux. Leaving the AWS light box illuminated without a film in place may degrade reviewing quality of images displayed on the monitor.

- Only images produced by GE-recommended laser cameras can be used for final interpretation of examinations. For compatible printers, see the latest product data sheets for this system, which you can obtain from your local sales representative.

- The three-section table is not designed to hold items in excess of 20 kg weight.

- Never make a clinical examination without either the Bucky or the Breast Holder or the Magnification stand fitted; the unprotected edge of the Digital Detector may damage sensitive skin when compression is applied.

- Breast compression of at least 3 daN (30 Newtons or 6.7 pounds) is essential in AOP mode.

- The AWS Cart is mounted on wheels so that it can be easily positioned for maximum convenience in the examination room. It should NOT be considered a "mobile" unit. Take great care if you must move it in the vicinity of any person or equipment. Do not move it during an examination.

- The monitor should be used in a suitably dark environment when reviewing a digital image. The optimum ambient light level is 50 lux.

- NEVER switch off at the Uninterruptible Power Supply (UPS) except in emergency (risk of data loss).

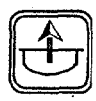
- To assure continued high level operation of the Senographe 2000D, the recommended quality control procedures should be followed.

- All measurement values refer to measurements made at the image plane. When magnification mode is used, the zoom factor is NOT taken into account. All processed images in Medical Application are in log format. All raw images in RWS are in linear format. The displayed measurements represent the lengths and areas of the graphic annotations made by the user, not the real length or surface area of the pathologies displayed on the screen.

- Annotations added by the operator on the Acquisition Workstation will be lost during image transfer to the Review Workstation.

- In AOP mode, only use a 19 x 23 cm paddle. The use of all other paddles is only permitted in Manual mode. In AOP mode, the automatic calculation of administered dose will only be accurate if the 19 x 23 cm paddle (specific to the Senographe 2000D) is used. Paddles that are NOT to be used in AOP mode are labeled with the following symbols:

- Markers larger than 2 mm^2 should not be present in the ROI. Large markers will affect the calculation of tissue density, which may lead to a degraded image.

- After exposure press  (located on the right of the Control Console) for decompression if the automatic decompression is not set in the program.

- In the absence of the compression paddle, leave the space free between the bottom of the paddle arm and the top of the image receptor assembly.

- To avoid image loss, never touch the recordable surface of a recordable CD (CD-R). Handle the disk only by the outer edge. Do not place it face down on a hard surface. Fingerprints or scratches will make the disk unusable. Before usage, verify that CD-R surface has no visible scratches. If there are any scratches, do NOT use the CD-R.

Senographe 2000D Review Workstation

- The Senographe 2000D Review Workstation has not been cleared by the FDA for final interpretation of examinations. Final interpretations should be done from hard copy films only.

- The monitor should be used in a sufficiently dark environment (optimum ambient light level of 50 lux) when reading a digital image.

- Should it ever be necessary to remove all power from the workstation (for maintenance, or to move the workstation), workstation database corruption may occur if the following procedure is not used: You MUST first bring the workstation to the **Shutdown** state as

described in Section 3 of the Operator's Manual. Once the system is completely shut down, switch off the equipment in this order: workstation computer unit; monitors; external CD-ROM device; external hard disk unit (option); filming interface unit (option); and keypad.

- When saving images on a CD, it is strongly recommended that no other operation should be performed. For a full CD-R the save operation can take up to 45 minutes.

For Device

Senographe 2000D

- If the digital detector casing is punctured, it must be removed by authorized GE Service personnel wearing protective gloves and dust masks; send the protective items for disposal along with the defective detector.

- Only Senographe 2000D recommended accessories should be used with this equipment. Failure to heed this warning may cause unexpected functions and possible data loss.

- Software programs other than those supplied by General Electric Medical Systems specifically for use with this system must NOT be loaded onto the system.

- The Interchange Media option is NOT recommended for permanent archiving. GE does not guarantee the suitability of the media for such purposes.

Senographe 2000D Review Workstation

- The Interchange Media option is NOT recommended for permanent archiving. GE does not guarantee the suitability of the media for such purposes.

- The Review Workstation monitors are unshielded. Placing them in a high magnetic field (e.g., near an MR system magnet) can cause permanent damage, and may void the warranty.

For Cleaning And Disinfection

Senographe 2000D

- CIDEX (a cleaning solution) contains glutaraldehyde. Direct contact is corrosive to exposed tissue, causing eye damage and skin irritation/damage. Do not get into eyes, on skin or on clothing. Use in well ventilated area and store in closed containers.

- Adequate cleaning and disinfection is necessary to prevent disease transmission. Be sure to thoroughly clean and disinfect equipment surfaces that contact the patient and all equipment surfaces likely to become soiled during use.

- Improper cleaning methods or the use of certain cleaning and disinfecting agents can damage the equipment, cause poor imaging performance or increase the risk of electric shock. To avoid possible injury or equipment damage:

  - Do not use harsh detergents, abrasive cleaners, high alcohol concentration or Methanol at any concentration. If skin preparations contain high alcohol concentrations, allow sufficient drying time before applying compression;

  - Do not expose equipment parts to steam or high temperature sterilization;

  - Never allow liquids to enter the internal parts of the equipment. Do not apply cleaning sprays or liquids directly to the equipment; always use a clean cloth dampened with the spray or liquid. If you become aware of liquid entry, disconnect the electrical supply and have the equipment checked by qualified service personnel before returning it to use.

- Always follow the germicide manufacturer's instructions and precautions for mixing, storage, method of application, contact time, rinsing requirements, protective clothing, shelf life and disposal to help assure effective and safe use of the product.

Potential Adverse Effects

The following is a list of potential adverse effects that apply to mammography and are also applicable to digital mammography using the Senographe 2000D system.

- Excessive breast compression
- Excessive X-ray exposure
- Electric shock
- Infection
- Skin irritation, abrasions, or puncture wounds

SUMMARY OF CLINICAL STUDIES

A. Study Design and Objectives

A multi-center clinical trial of the Senographe 2000D full field digital mammography (FFDM) device was conducted in the United States comparing results obtained with the Senographe 2000 D to results obtained with screen-film mammography (SFM) systems.

The objective of the study was to test the non-inferiority of Senographe 2000D compared to SFM in a mixed diagnostic and screening population. Sensitivity, receiver operating characteristics (ROC), and specificity analyses were performed. A side-by-side feature comparison was also performed.

B. Study Population

- Cancer cases were identified from a diagnostic cohort and a screening cohort. The diagnostic cohort consisted of 605 women presenting for diagnostic mammography.

- Six hundred twenty-five (625) women (44 cancer cases and 581 non-cancer cases) were included in the combined study cohort.

- Fifty-five percent (55%) (24/44) of the cancer cases in the study cohort were derived from a diagnostic population and forty-five percent (45%) (20/44) were derived from a screening population. The study population provided adequate information about use of the device in a diagnostic population and provided some additional information about use of the device in a screening population. While this study cohort was a mixture of diagnostic patients and screening cancers, the distribution of cancer stages and sizes was not statistically different from that of a screening population.

- Sixty-one percent (61%) of the cancers in the study were Stage 0 or I. Thirty-nine percent (39%) were Stages II, III, and IV. Forty-three percent (43%) of the cancers were less than or equal to 1 cm; fifty-seven percent (57%) of the cancers were larger than 1 cm.

C. Results

- Receiver Operating Characteristic (ROC) curve area was 0.722 for Senographe 2000D versus 0.723 for SFM. Based on the 95% confidence interval for the difference between ROC curve areas, the ROC curve area of Senographe 2000D could be as much as 0.073 below, to as much as 0.055 above, that of SFM. Thus the null hypothesis that the ROC curve area of Senographe 2000D was lower than that of SFM by more than 0.10 was rejected ($p<0.0001$).

- Sensitivity was 68% for Senographe 2000D versus 70% for SFM, for all cancer stages and sizes. Based on the 95% confidence interval for the difference in sensitivities, the sensitivity of Senographe 2000D could be as much as 9.96% below, to as much as 7.24% above, that of SFM. Thus the null hypothesis that the sensitivity of Senographe 2000D was lower than that of SFM by more than 10% was rejected ($p=0.0245$).

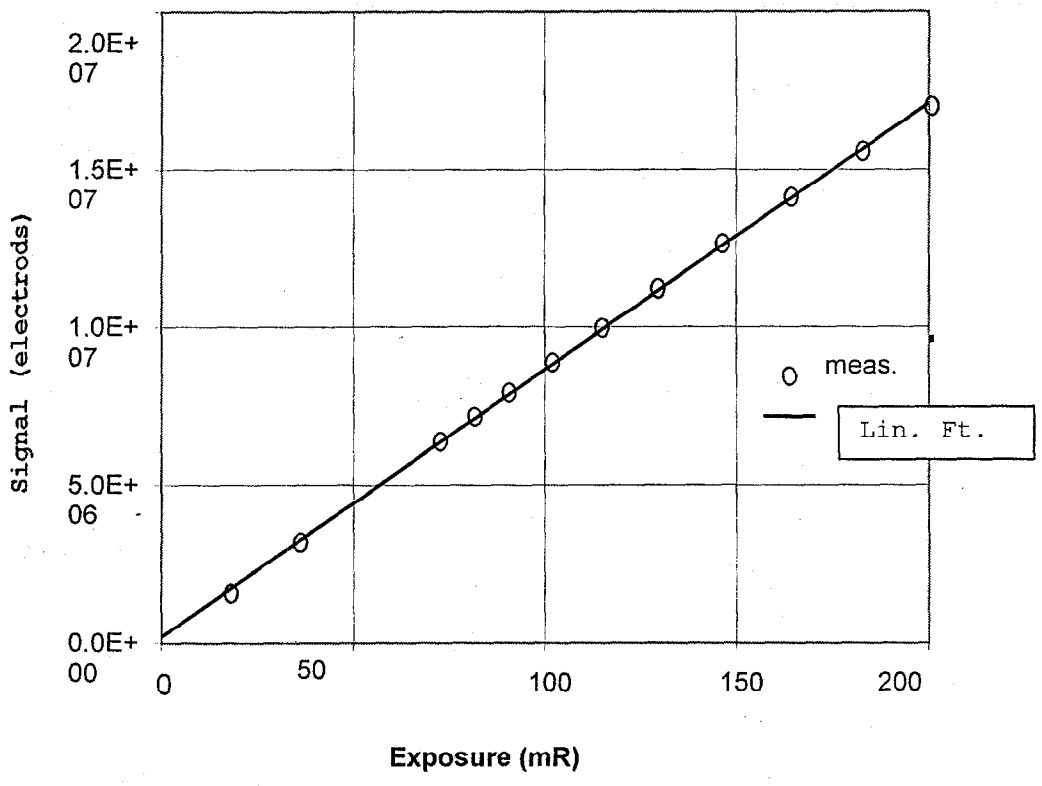
- Specificity was 55% for Senographe 2000D versus 53% for SFM, for all cancer stages and sizes. Thus the recall rate in this study for lesions that turned out to be benign was 45% for Senographe 2000D versus 47% for SFM. Based on the 95% confidence interval for the difference in specificities, the specificity of Senographe 2000D could be as much as 0.58% below, to as much as 4.36% above, that of SFM. Thus the null hypothesis that the specificity of Senographe 2000D was lower than that of SFM by more than 5% was rejected ($p<0.001$).

- Side-by-side feature comparison data demonstrated that Senographe 2000D allows better visibility of tissue at the skin line than SFM and that Senographe 2000D is equivalent to SFM for lesion conspicuity and visibility of tissue at the chest wall.

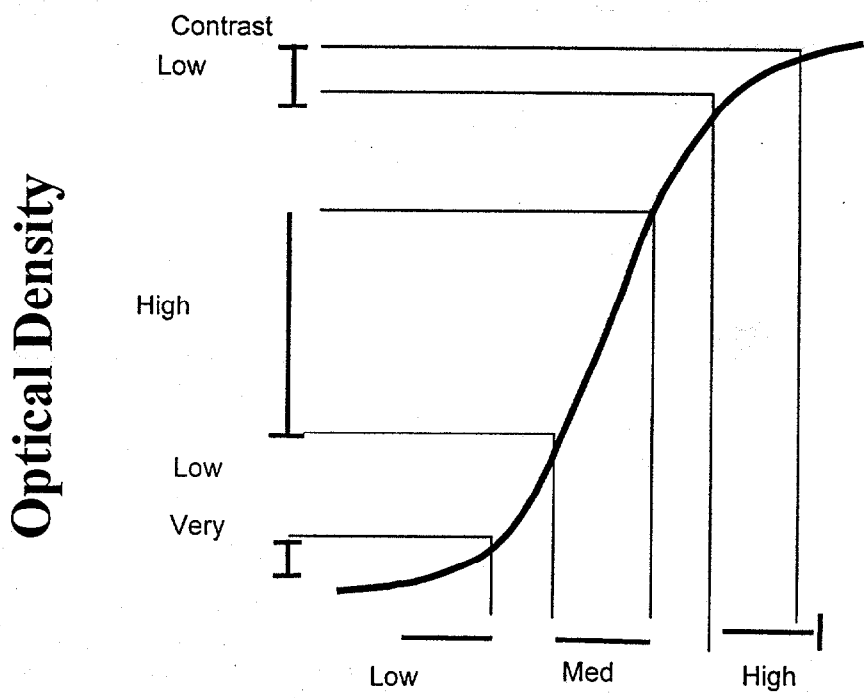
NONCLINICAL STUDIES

A. Dynamic Range and Sensitometric Response

The detector exhibits a response that is linear over a range of 0 to 153 mR at the breast support surface. The range of exposure over which linear response is achieved is at least 3 times larger than the linear portion of a SFM sensitometric curve.



Digital Detector Response



Film / Screen Response

B. Detective Quantum Efficiency (DQE)

DQE measures the efficiency by which a system transfers signal and noise. It is defined as the ratio of the square of input signal-to-noise ratio (SNR) to the square of input SNR. Since the output SNR is a measure of the displayed image quality and the input SNR can be related to patient dose, DQE can be considered as a ratio of image quality to patient dose. Doubling DQE means that one gets the same image quality at half the dose or a 40% improvement in image quality for the same dose.

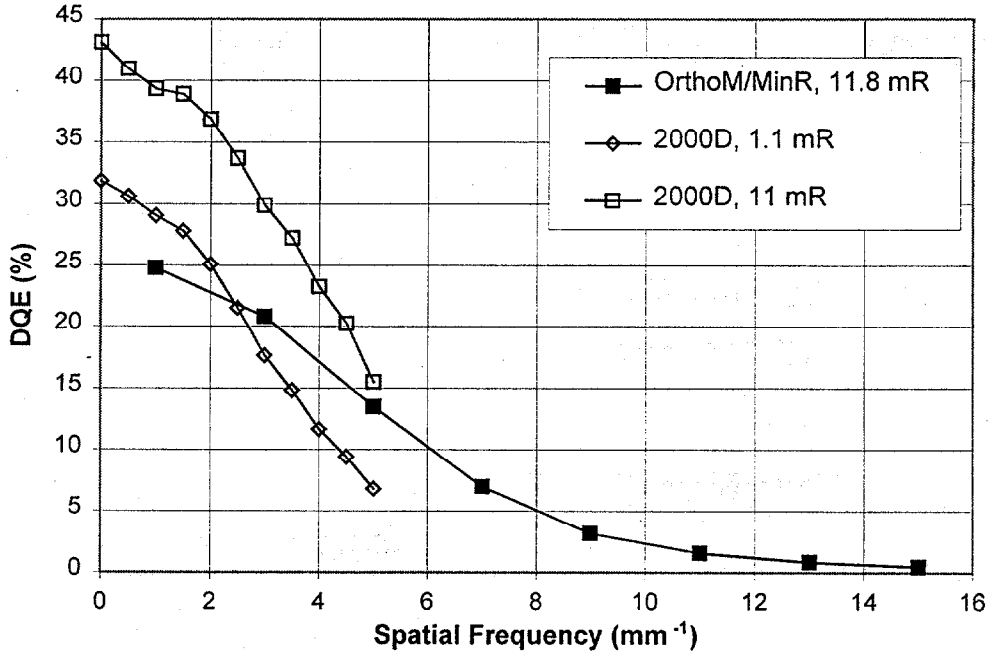
$$DQE = \frac{SNR^2 \text{ at detector output}}{SNR^2 \text{ at detector input}} \propto \frac{\text{Image Quality}}{\text{Patient Dose}}$$

where SNR = signal-to-noise ratio

C. Comparison of Senographe 2000D and SFM DQE

At detector exposure levels characteristic of those used in screen-film mammography (10 to 15 mR), the DQE of the Senographe 2000D exceeds that of common screen-film systems throughout the 0 to 5 cycle/mm range. Even at 1 mR, the low-frequency DQE of the Senographe 2000D exceeds that of screen-film systems when used at ten times the exposure level. While the DQE of screen-film systems extends to higher spatial frequencies, the output SNR is often dominated by film-grain noise and not quantum noise. Because of the essentially linear response of the Senographe 2000D detector, quantum-limited performance and substantially constant DQE are achieved over a wide range of exposure levels. DQE of Senographe 2000D exceeds that of SFM up to the 5 lp/mm Nyquist frequency.

DQE of the Senographe 2000D and a Screen-Film System

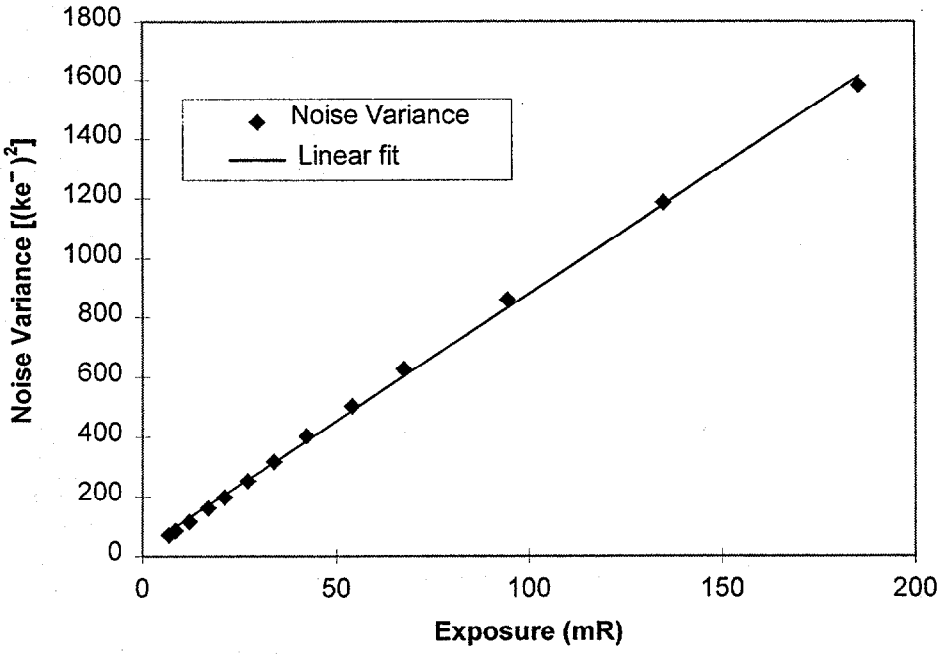


All Senographe 2000D DQE measurements shown here were made using 30 kVp, Rh anode track, Rh filter, and added filtration of 1.5 cm acrylic plus 3 mm Al. Exposures at the detector entrance plane are included with the data.

D. DQE versus Exposure Level - Quantum-Limited Performance

The detector of the Senographe 2000D not only exhibits a linear signal response over a wide exposure range, it also exhibits a quantum-limited noise response. Quantum-limited response is evidenced by image noise variance (the square of the standard deviation of the pixel values within a region of interest) that increases linearly with the exposure to the detector.

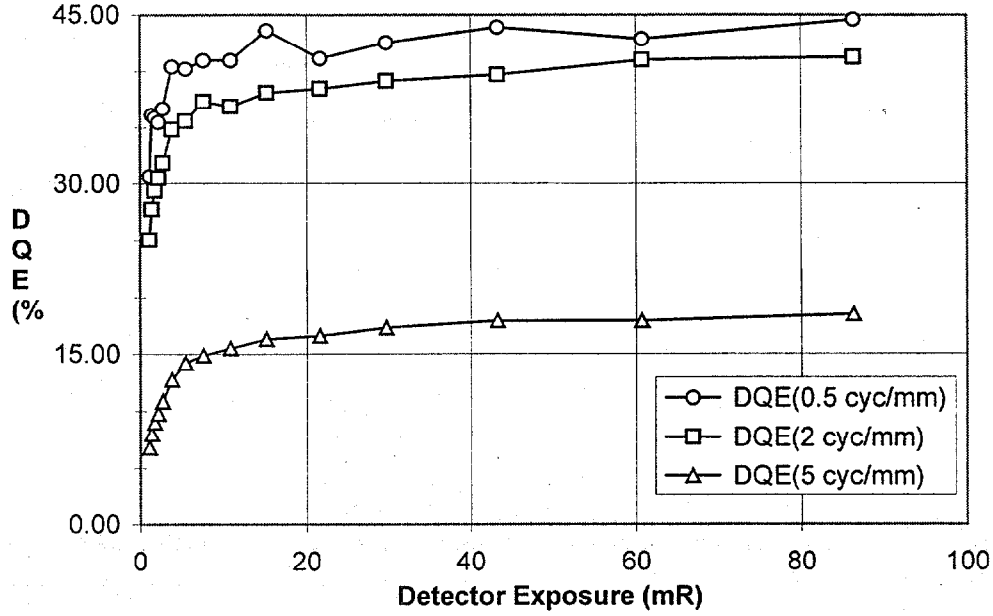
Image Noise vs. Exposure for the Senographe 2000D



At low exposure levels, the plot of image noise variance vs. exposure commonly deviates from a straight line due to the influence of noise in the imaging system. For the Senographe 2000D, this deviation is not evident until the exposure at the detector is less than about 3 mR.

The combination of linear signal response and quantum-limited noise response leads to a DQE that is independent of exposure level over a broad range of exposures. Unlike screen-film systems, which tend to have low DQE at high film densities (near the skin line) and at low film densities (in the image of glandular tissue or near the chest wall), the Senographe 2000D provides uniformly high DQE throughout the mammogram. This provides a probability of detection of an abnormality that is less dependent on its location than is the case for screen-film detectors.

DQE vs. Exposure at Three Spatial Frequencies



DQE is essentially independent of exposure for exposures at the detector plane greater than about 3 mR. Therefore, the Senographe 2000D DQE has little dependence on the exposure level for the clinical exposure range.

E. Conclusions

The range of linear signal response for the Senographe 2000D is significantly better than that of screen film.

The detective quantum efficiency (DQE) for the Senographe 2000D is comparable to or higher than screen film up to its Nyquist frequency (5 lp/mm), though beyond that frequency the Senographe 2000D gives no meaningful information.

Below the Nyquist frequency, for exposures that are typical near the skin line or in a dense area of the breast, the Senographe 2000D has a DQE that is higher than that of screen-film by a factor of 2 to10. Furthermore, at these spatial frequencies the Senographe 2000D has nearly constant DQE over the range of exposures commonly found in a mammogram, while that of screen-film varies by a factor of 3 to 5 between the mid- and high-density regions

While the higher DQE for the Senographe 2000D at spatial frequencies less than or equal to the Nyquist frequency suggests the possibility that mammograms may be taken at a lower radiation dose, particularly in dense breasted women, the accuracy of mammographic interpretation at lower doses has not been studied to determine whether the absence of information above the Nyquist frequency is clinically important.

The combination of linear signal response and quantum-limited noise response leads to a DQE that is independent of exposure level over a broad range of exposures. Unlike

screen-film systems, which tend to have low DQE at high film densities (near the skin line) and at low film densities (in the image of glandular tissue or near the chest wall), the Senographe 2000D provides uniformly high DQE throughout the mammogram. This provides a probability of detection of an abnormality that is less dependent on its location than is the case for screen-film detectors. This was shown to be true by the side-by-side feature comparison (see section I of CLINICAL STUDIES).

- The Senographe 2000D has wider exposure latitudes, higher DQE, allows for electronic archival transmission and image manipulation, and involves shorter examination time. The ability to manipulate images has the potential to eliminate the need for additional magnification of views. Similarly, windowing and leveling can compensate for exposure variations eliminating the need for repeated exposures or exposures adjusted to specifically view the skin line or the chest wall.

CLINICAL STUDIES

A. Study Design and Objectives

A multi-center clinical trial of the Senographe 2000D full field digital mammography (FFDM) device was conducted in the United States comparing results obtained with the Senographe 2000D to results obtained with screen-film mammography (SFM) systems.

The objective of the study was to test the non-inferiority of the Senographe 2000D compared to SFM in a mixed diagnostic and screening population. Sensitivity, receiver operating characteristics (ROC), and specificity analyses were performed. A side-by-side feature comparison was also performed.

B. Study Population

Women aged 40 or older attending for diagnostic mammography were included in the study. Women were excluded from the study if they were pregnant or suspicious of being pregnant; had breast implants; had breasts too large to be adequately positioned on a 24 x 30 cm screen -film receptor; had non-focal or bilateral breast pain; or who were unable or unwilling to execute the consent form.

Six hundred twenty-five (625) women (44 cancer cases and 581 non-cancer cases) were included in the study cohort. Cancer cases were identified from a diagnostic cohort and a screening cohort. The diagnostic cohort consisted of 605 women presenting for diagnostic mammography at four sites [the University of Colorado Health Sciences Center (UCHSC), the University of Massachusetts Medical Center (UMMC), Hospital of the University of Pennsylvania (HUP), and Massachusetts General Hospital (MGH)]. This population included 24 diagnostic cancer cases. The screening cohort consisted of 20 consecutive cancer cases generated from a screening population of over 4,000 women. The screening cohort was conducted at UCHSC and UMMC.

Fifty-five percent (55%) (24/44) of the cancer cases in the study cohort were derived from a diagnostic population and forty-five percent (45%) (20/44) were derived from a screening population. The study population provided adequate information about use of the device in a diagnostic population and provides additional information about use of the device in a screening population. While this study cohort was a mixture of diagnostic patients and screening cancers, the distribution of cancer stages and sizes was not statistically different from that of a screening population.

C. Demographics

The average age for the women in the study was 55 years with a range from 40-86 years. Eighty-five percent (85%) of the women were white, 8% were African-American, 2% Hispanic, 1% Asian, and 4% unknown. Thirty-four percent (34%) of the women reported a history of breast-related medical diseases or conditions and 33% reported a history of hormone replacement therapy.

D. Image Acquisition and Interpretation

Two views, craniocaudal (CC) and mediolateral (MLO), of each breast were acquired by each modality using GE Medical Systems' (GEMS) Senographe 2000D system with equal or slightly lower breast doses than SFM. Equivalent target-filter, kVp, and equal or slightly lower mA values were used on the Senographe 2000D. The same technologist performed both the Senographe 2000D and SFM imaging with similar positioning and compression forces. Fifty-nine percent (59%) were bilateral exams and 41% were unilateral exams.

Five MQSA-qualified radiologists independently interpreted each SFM and Senographe 2000D image. The radiologists had no prior knowledge of the cases. Senographe 2000D images were stored digitally and printed at UCHSC and UMMC to provide comparability to SFM. Each radiologist interpreted half the SFM cases first and half the Senographe 2000D cases first, with at least 30 days between interpretations of the same case from each of the two modalities. For each case, the radiologist provided BIRADS categories (0, 1, 2, 3, 4, or 5) and a probability of cancer on a 0-100% scale for BIRADS 0, 3, 4, and 5 breasts.

E. Cancer Stage and Size Distribution

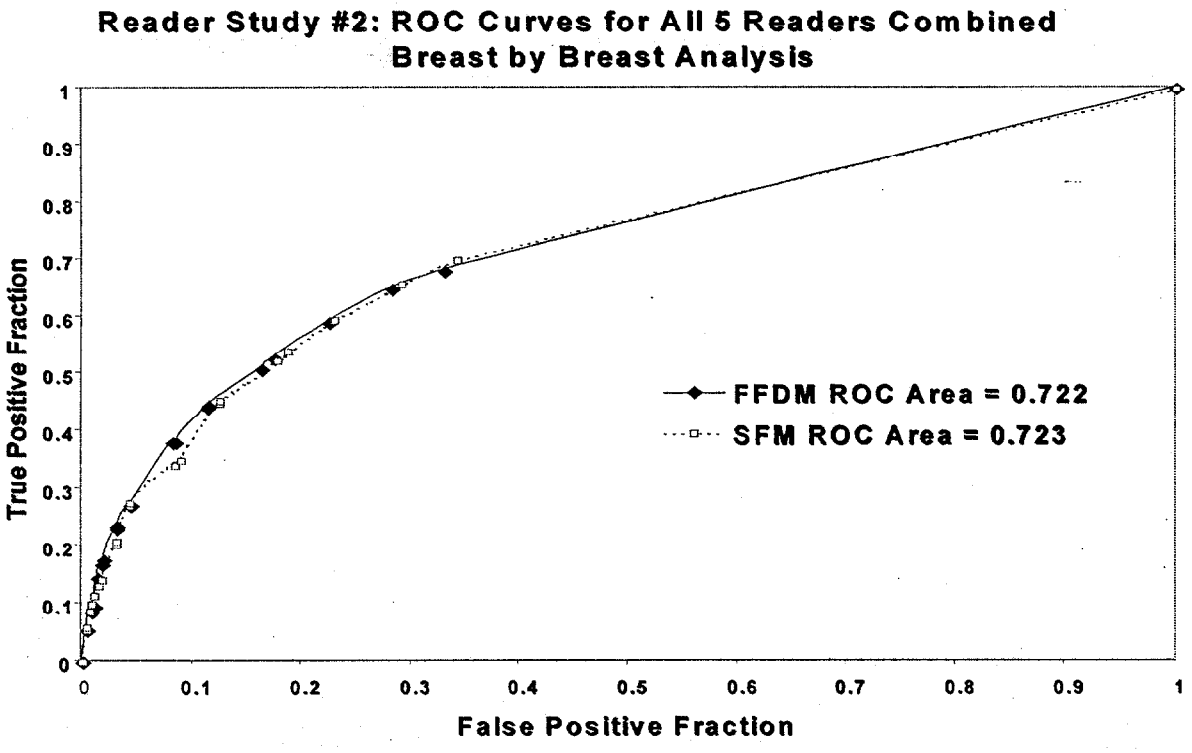
Sixty-one percent (61%) of the cancers in the study were Stage 0 or I. Thirty-nine percent (39%) were Stages II, III, and IV. Forty-three percent (43%) of the cancers were less than or equal to 1 cm; fifty-seven percent (57%) of the cancers larger than 1 cm.

The Agency for Health Care Policy and Research (AHCPR) Clinical Practice Guidelines recommend that in a good mammography program at least 50% of detected cancers should be Stage 0 or I and at least 30% of detected cancers should be less than or equal to 1 cm in size. The percentage of Stage 0 and I cancers in this study exceeded the AHCPR guideline for Stage 0 and I cancers by 11% and exceeded the AHCPR guideline for small cancers by 13%.

F. ROC Curve Results

ROC curves were constructed from all cases assigned a BIRADS code of 0, 3, 4, or 5, using independent interpretations of Senographe 2000D and SFM based on the probabilities of cancer (on a 0-100% scale). ROC curve areas were 0.722 for Senographe 2000D versus 0.723 for SFM.

Based on the 95% confidence interval for the difference between ROC curve areas, the ROC curve area of Senographe 2000D could be as much as 0.073 below, to as much as 0.055 above, that of SFM. Thus the null hypothesis that the ROC curve area of Senographe 2000D was lower than that of SFM by more than 0.10 was rejected ($p<0.0001$).


Reader Study #2: ROC Curves for All 5 Readers Combined
Breast by Breast Analysis
True Positive Fraction
False Positive Fraction
FFDM ROC Area = 0.722
SFM ROC Area = 0.723
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

G. Sensitivity Results

A comparison was made of the fraction of total cancers among the study cohort that were detected by Senographe 2000D and SFM, giving an estimated sensitivity for each modality. For all cancer stages and sizes, the sensitivity was 68% for Senographe 2000D compared to 70% for SFM, for all cancer stages and sizes.

Based on the 95% confidence interval for the difference in sensitivities, the sensitivity of Senographe 2000D could be as much as 9.96% below, to as much as 7.24% above, that of SFM. Thus the null hypothesis that the sensitivity of Senographe 2000D was lower than that of SFM by more than 10% was rejected ($p=0.0245$).

H. Specificity Results

Specificity was 55% for Senographe 2000D versus 53% for SFM, for all cancer stages and sizes. Thus the recall rate in this study for lesions that turned out to be benign was 45% for Senographe 2000D versus 47% for SFM.

Based on the 95% confidence interval for the difference in specificities, the specificity of Senographe 2000D could be as much as 0.58% below, to as much as 4.36% above, that of SFM. Thus the null hypothesis that the specificity of Senographe 2000D was lower than that of SFM by more than 5% was rejected ($p<0.001$).

I. Side-by-Side Feature Comparison

The side-by-side feature analysis comparison included 40 cancer cases. All 40 cases had MLO comparisons and 39 had CC comparisons for a total of 79 views. Both Senographe 2000D and SFM images were placed on the same mammography alternator or bank of viewboxes. Five (5) independent MQSA-qualified radiologists evaluated lesion conspicuity, inclusion of tissue along the chest wall, and visibility of tissue at, or near, the skin line of the breast using an 11-point Likert scale (0-4 favoring Senographe 2000D, 5 equally visible on Senographe 2000D and SFM, 6-10 favoring SFM). An overall mean value was calculated across all readers and views.

For visibility near the skin line, readers could see tissue at the skin line better with Senographe 2000D than with SFM (mean value of 2.95). Lesion conspicuity and tissue at the chest wall were equally visible with mean values of 5.17 and 5.21, respectively. Readers could, on average, discriminate calcifications, masses, architectural distortions, and focal asymmetry equally well on Senographe 2000D and SFM.

J. Safety

No adverse consequences (serious or otherwise) were reported for patients enrolled during the study.

K. Conclusions

- Data derived from clinical trials, in conjunction with preclinical data on the physical parameters of the system, provide reasonable assurance that the Senographe 2000D system is safe and effective for use in screening and diagnosis of breast cancer.

- The ROC curve areas for the Senographe 2000D and SFM systems are virtually identical.

- The sensitivity analysis demonstrated that the Senographe 2000D has a sensitivity comparable to that of SFM in the screening and detection of breast cancer.

- The specificity analysis demonstrated that the Senographe 2000D system results in fewer women being recalled than SFM.

- The side-by-side feature comparison data demonstrated that the Senographe 2000D system allows better visibility of tissue at the skin line than SFM and that the Senographe 2000D system is comparable to SFM for lesion conspicuity and visibility of tissue at the chest wall.

CONFORMANCE TO STANDARDS

The GE Medical Systems Senographe 2000D system meets the following standards:

- IEC 601-1: Medical electrical equipment - General requirements for safety (cert. N° 0004/601.1/15 for Senographe 2000D and cert. N° 0004/601.1/13 for Acquisition WorkStation in Annex).

- IEC 601-1-1: Medical electrical equipment — Collateral standard: Safety requirements for medical electrical systems (cert. N° 0004/601.1.1/27 in Annex).

- IEC 601-1-2: Medical electrical equipment — Collateral standard: Electromagnetic compatibility for medical electric systems (AC N° 032/AF-99-40137 for Senographe 2000D and AC N° 033/AF-99-40138 for Review WorkStation in Annex).

- IEC 601-1-3: Medical electrical equipment — Collateral standard: Requirements for radiation protection in diagnostic X-ray equipment (cert. N° 004/601.1.3/5 in Annex).

- IEC 601-2-32: Medical electrical equipment — General requirements for Safety (cert. N° 0004/601.2.32/8 in Annex).

- IEC 601-2-45: Medical electrical equipment — Particular requirements for the safety of mammography X-ray equipment (cert. N° 0004/601.2.45/1 in Annex).

- IEC 601-1-4: Medical electrical equipment — Collateral Standard: programmable electrical medical systems.

- IEC 905: Safety of information technology equipment (Review Workstation)

TRAINING PROGRAM

Users must ensure that they receive training on the Senographe 2000D with GE Medical Systems training programs prior to use on patients. GE Medical System training programs will address the new MQSA training regulations in product labeling to ensure that prospective users are aware of the required eight hours of training for any medical physicist, technologist, or interpreting physician. *The recommended training program is documented in the Operator's Manual.*

OPERATOR MANUAL/DIRECTIONS FOR USE

A copy of the table of contents from the Senographe 2000D and Senographe 2000D Review Workstation Operator Manuals are provided on the following pages. The user should refer to the Operator Manuals for directions on how to use the Senographe 2000D system.

PRODUCT COMPLAINTS

Any health care professional (e.g., customer or user of this system of products) who has any complaints or has experienced any dissatisfaction in the quality, durability, reliability, safety effectiveness and/or performance of this product, should notify GEMS. If the device malfunctions and may have caused or contributed to a serious injury of a patient, GEMS should be notified immediately by telephone, fax, or written correspondence.